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Identification of early, modifiable predictors of cardiometabolic risk and impacts of family-based stress on child obesity

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Dissertation

IDENTIFICATION OF EARLY, MODIFIABLE PREDICTORS OF CARDIOMETABOLIC RISK AND IMPACTS OF FAMILY-BASED STRESS ON CHILD OBESITY

by

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Inquiries

Launched brightly

Land sprightly

On numbers and ideas

Woven as fibers

Of creativity and truth

Spun into growth of

An answer, energetic

With more questions

To launch

-S.E. Ferreira

DEDICATION

I would like to dedicate this work to my husband Brian, and my parents Tawakol and Mely, for their inspiration, love, and encouragement.

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IDENTIFICATION OF EARLY MODIFIABLE PREDICTORS OF CARDIOMETABOLIC RISK AND IMPACTS OF FAMILY-BASED STRESS ON CHILD OBESITY

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ABSTRACT

Childhood obesity puts children at risk for chronic metabolic diseases. Identification of weight-related risk factors in childhood is important to prevent adult cardiovascular disease (CVD). This dissertation evaluates risk factors for adolescent obesity and dyslipidemia. Multivariable regression analyses of data from black and white girls in the National Growth and Health Study (n=2,379) were used to identify predictors of these cardiometabolic risks (CMR). The first aim was to compare the impact of different measures of early adolescent adiposity (body mass index, BMI; waist circumference, WC; waist-to-hip ratio, WHR; percent body fat from bioelectrical impedance, %BF) as predictors of later adolescent lipid levels. Black girls had significantly lower pre-adolescent %BF (23.6% vs. 26.4%) than whites, but gained fat more rapidly (34.7% vs. 14.0% increases), exceeding whites in %BF by late adolescence. WC was a stronger

predictor of subsequent low-density lipoprotein (LDL) levels than other measures of body composition (LDL difference between WC of highest and lowest quintiles: 29.5 mg/dL, whites; 17.9 mg/dL, blacks). Regardless of race, BMI was associated with lower levels of high-density lipoprotein (HDL), and higher levels of LDL, TG, and TG/HDL (triglyceride to HDL ratio). The second aim compared pre- and post-menarche measures of early adolescent body fat as determinants of later LDL, HDL, TG, and TG/HDL. BMI measures post-menarche were generally better predictors of later lipids in white girls compared with pre-menarche measures, while pre- and post-menarche BMI measures were equally good as predictors of later lipid levels in black girls. The third aim examined the role of maternal depressive symptoms as a risk factor for increased BMI among daughters. Daughters of mothers with higher depression scores had greater BMI increases throughout adolescence ($p<0.0001$), and a late adolescent BMI that was 0.88 kg/m^2 higher than those of mothers with lower depression scores. These findings underline the importance of monitoring early physical and psychosocial CMR factors during adolescence to prevent CVD risk.

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LIST OF ABBREVIATIONS

%BF ..... Percent Body Fat

ANOVA ..... Analysis of Variance

ANCOVA ..... Analysis of Covariance

BIA ..... Bioelectric Impedance Analysis

BMI ..... Body Mass Index

BU ..... Boston University

CMR ..... Cardiometabolic Risk

DASH ..... Dietary Approaches to Stop Hypertension

DXA ..... Dual Energy X-ray Anthropometry

FFM ..... Fat-Free Mass

HAQ ..... Habitual Activity Questionnaire

HBP ..... High Blood Pressure

HEI-2015 ..... Healthy Eating Index 2015

HDL ..... High Density Lipoprotein

IOTF ..... International Obesity Task Force

IR ..... Insulin Resistance

LDL ..... Low Density Lipoprotein

LDL-C ..... Low Density Lipoprotein Cholesterol

MET .....Metabolic Equivalent

NCEP ..... National Cholesterol Education Program

NDS .....Nutrition Data System, University of Minnesota

NGHS.....National Heart Lung and Blood Institute's Growth and Health Study

NHANES..... National Health and Nutrition Examination Survey

NHLBI.....National Heart Lung and Blood Institute

PDAY ..... Pathological determinants of atherosclerosis in youth

SES..... Socioeconomic Status

TBF .....Total Body Fat

TG..... Triglycerides

TV ..... Television

TG/HDL..... Triglyceride to HDL ratio

USDA ..... United States Department of Agriculture

WC..... Waist Circumference

WHtR ..... Waist to Height Ratio

WHR.....Waist to Hip Ratio

CHAPTER ONE: Introduction

1.0 The Child Obesity Epidemic and Burdens of Risk

Childhood obesity is an epidemic in the United States as well as worldwide and the costs are great; every year, it puts children on a trajectory leading to chronic metabolic diseases(1–9). As in the case of adult obesity, the social and physical environment influences child obesity risk via eating and activity behaviors(10–12). Further, children of different races and socioeconomic statuses carry differential burdens for obesity risk(2,13–15). This secondary analysis of the National Growth and Health Study (NGHS) adolescent population addresses some important gaps in knowledge concerning the identification of racial differences in childhood predictors of obesity and cardiometabolic outcomes in the United States.

1.1 Socio-Environmental Context – Obesity-Related Health Risks at Home

Childhood eating behaviors(16–18) are shaped by socio-environmental factors in the home(19,20) and are a natural starting point to consider as predictors of the outcomes of diet quality(19,21) and the later development of obesity (20) and chronic diseases. These eating behaviors are usually first learned within the home and in the socio-environmental context of the family(11,17,22)

during family meals(23–25). While the home can be a safe and supportive place, in certain families who face social or economic stressors(26), the home can also be a source of tremendous stress during developmental periods(27) wherein children learn how and what to eat(28–31). The theory behind the effects of social and environmental factors on child weight status has been well-established(16,22,32–35). Socioeconomic status (SES) and parental education are two resources that shape the environment of growing children and have been more extensively studied. However, obesity risk has not been well studied longitudinally in the context we propose, integrating well-established early adolescent predictors in a broader socio-environmental context of potential cardiometabolic risk factors.

1.2 Adolescents: A Vulnerable Population

Adolescents represent a population of youths vulnerable to new, unhealthy behaviors. Not quite children, and not quite adults, there are many social, physical, and psychological changes that happen during adolescence. Some view adolescence as a sensitive period – not unlike the first 1,000 days of a baby's life(36) – in which changes in brain architecture(37) can result in behavioral changes and perhaps have lasting effects on biology(38). While more

well established practices exist for classification of adult cardiovascular disease, defining metabolic syndrome, or identifying who may be at higher risk of later CVD (39) in children and adolescents is controversial. Cardiovascular diseases include myocardial infarction, stroke, and coronary heart disease(40). A number of studies in adults employ the well-established Framingham Cardiovascular Risk Score(41–44) or American Heart Association Cardiovascular Health Score(45) alongside various associated risks. Studies in younger populations have, however, shifted away from classifying metabolic syndrome to a more detailed look at both individual and combined mechanisms for increased risk.

Cardiometabolic risk (CMR) is a term that describes four primary types of problematic metabolic statuses that increase the likelihood of a patient developing cardiovascular disease: 1) dyslipidemia, 2) hypertension, 3) obesity, and 4) dysglycemia(46). A number of studies addressed cardiometabolic risk outcomes by looking clusters of factors(47–52) in specific populations of children or adolescents. In one case, Okusun et al. computed cardiometabolic risk factor clustering scores (cMetS) in older American adolescents of varied racial-ethnic groups(53) including mean arterial blood pressure, triglycerides, fasting blood glucose, waist circumference, and high-density lipoprotein cholesterol and

examined trends in risk over time in the United States. In a small prospective study (n=434) which constructed an overall CVD clustered risk score among a young children starting from 6 years of age(54) to the beginning of adolescence, the results based on body fat were inconclusive. Camhi et al. examined the prevalence of CMR among adolescents, ages 12-18 years, in the National Health and Nutrition Examination survey(51), finding that risk factors clustered within BMI groups. Greater risk of CMR was associated with having higher BMI, lower income (in overweight but not obese adolescents). Predictive scores with early risk factors do exist for specific types of metabolic syndrome, such as diabetes(55) or obesity(56) or investigate specific biomarkers(57), but do not incorporate clusters of risk factors together.

1.3 Maternal Depression Symptoms are Toxic Stress Exposures for Children

Maternal depression symptoms are a psychosocial risk factor which is widespread in the United States(26,36,58,59). Further, women of ethnic minorities and low SES have fewer resources to cope with the frequent experience of adverse life events(26), and also exhibit the highest rates of maternal depression(60–63) and detriment to their mental health(64–66). SES may act as a stressor that adversely influences mental health of maternal

caregivers in a way(60,67,68) that challenges the bond between mothers and their children, and becomes a specific source of toxic stress to the child. Toxic stress is the most dangerous form of stress response resulting from frequent or prolonged activation of the body's stress response systems without the buffering protection of a supportive adult relationship(69).

Maternal depression(60–63) is a specific source of toxic stress in the home. When the child's physical stress response is no longer tolerable, it becomes toxic(69,70) and physiological changes may occur to the neuroendocrine system(65) with potential metabolic consequences: chronic stress interacts with mechanisms of energy intake and expenditure and may contribute to overweight and obesity. Not all stress is harmful: Boyce et al.(71) describe an interesting curvilinear hypothesis wherein high biological reactivity from experiencing early childhood traumas may be advantageous to either elevate sensitivity to stress cues, or to take advantage of environmental opportunities – but this may only be true in protective environments. In most cases, the relationship between early adversity and the child's psychological health may be dynamic, where health outcomes may be mediated in part by neurobiological effects of trauma. The extent to which depression or sense of self worth amongst children or

adolescents exposed to maternal depression mediates cardiometabolic risk is unclear. Many of the toxic stress exposures from compromised maternal mental health may predict obesity risk in children(72) via action on family mealtime practices(20,73,74) and childhood diet quality and activity-related behaviors(21,75).

1.4 Defining Adverse Childhood Experiences as Psychosocial Risk Exposures for Future Disease

The potential link between psychosocial stress in childhood and long-term effects on risk factors for adult cardiovascular disease risk has garnered recent attention(76). As many predictors of cardiovascular disease also have their roots in childhood, the extent to which early experience of psychological distress may impact long-term effects on later health and wellbeing requires further investigation(77,78). The Adverse Childhood Experiences (ACE) Study(79) was a pioneer in this field, with almost 10,000 adults reporting on prior experience of seven categories of ACEs during childhood: psychological, physical or sexual abuse, witnessing violence against their mother, or living with household members involved with substance abuse, mentally ill or suicidal, or imprisoned. These were referenced against standard medical evaluations for measures of

adult risk behavior, health status, and disease. Individuals with multiple ACE category exposures were likely to have multiple risk factors later in life, including: ischemic heart disease, cancer, chronic lung disease, skeletal fractures, and liver disease. A recent 2017 statement by the American Heart Association(80) separated specific ACEs into constructs that were associated with cardiometabolic outcomes individually or in composite scales. Notably, these factors included parental psychopathology and economic hardship. Studies have suggested that exposure to childhood adversity may be associated with obesity(81) or increased risk of hypertension(82–84). A meta-analysis of 41 studies(85) with 190,285 participants demonstrated that childhood maltreatment was associated with development of obesity risk over the life course (odds ratio=1.36, 95% CI: 1.26-1.47), although results of some of the included studies found that these adverse effects were attenuated with controlling for current adult depression. Childhood adversity has been documented as a factor that predisposes to inflammation and other biomarkers associated with cardiovascular disease. Chronic inflammation often accompanies obesity(85–87), and future investigation of inflammatory biomarkers could be useful to understand the mechanism of developing cardiometabolic risk in response to experience of childhood adversity.

In NGHS, using the Center for Epidemiological Studies Depression Scale (CES-D) at ages 16 and 18, adolescent depressive symptoms were associated with elevated BMI in young adulthood (ages 21-23), and especially in black girls(88). Other studies that focused on the child's own psychological state (as opposed to association with exposure to mother's mental health symptoms) found associations between phobia, panic, anxiety, or depression disorders and later obesity(88) or hypertension(89), but did not explore other contributors to intrinsic psychological wellness which could buffer the effects of challenges to a child's mental health, such as the child's sense of self worth.

1.5 The Unknown Effect of Maternal Depression on Adolescent Obesity

By contrast, healthy social relationships, such as those in a family, can buffer against adversity and support positive health(90). Proper nutrition and dietary patterns(91–93) - including nutritional content, diet variety, and diet diversity, as well as physical activity are among the lifestyle behaviors which are associated with well-being(94). These are also important predictors of childhood obesity and cardiometabolic risk(95) that could be impacted by psychosocial environment in the home. Studies that assessed adversity in childhood or

adolescence examined influences of peer bullying, or abuse or neglect at home(85–87,96–102), and have not focused on maternal depression and child obesity risk. Prior cross-sectional work in the area of maternal factors and effects on child weight status and obesity risk has focused on early years(103,104) launching a recent burst of research and interventions focusing on the first 1,000 days of a child's life(105,106). By contrast, recent work in the Add Health cohort(87) of 132 schools of older adolescents with an average age of 15 years considered the role of SES and the maternal-adolescent relationship by asking both mothers and the adolescents questions about perceived closeness and then examining long-term cardiovascular risk, showing the importance of the social context to child health: concentration of poverty at school, compounded with parent's education are associated with adolescent overweight. Another study in NHANES(64) examined the impact of food security combined with poor maternal mental health in low-income children ages 3-17, finding that the presence of maternal stressors elevated risk of overweight of the children. However, little is known specifically about any enduring effects of maternal depression on a child's body weight as they mature into young adults(58). Particularly, the independent, long-term effects, if any, of maternal depression as

a predictor of the outcome of obesity risk in black and white adolescent girls of different socioeconomic statuses are not known.

1.6 Anthropometric Indicators of Obesity in Children

Physical predictors of cardiometabolic risk include relatively simple measures of adiposity(107,108) such as body mass index (BMI) and waist circumference. While BMI has been used in clinical settings to predict a child's propensity for obesity and associated metabolic risk, the limitations of BMI are apparent. BMI does not capture sources of body fat, particularly depots of visceral adipose tissue that are highly associated with metabolic disease(109). The utility of waist size as a predictor of health risk in youths is supported in a few smaller studies, including an understudied group of minority youths (ages 2-19 years) from Central and South America and the Caribbean(110) and Scottish boys (14-16 years)(111). Waist size has been proven useful to highlight disparities between black and white adults (112). Prior work in NGHS showed that girls who were overweight (at 9 years) in childhood were 11-30 times more likely to be obese in adulthood (at 21-23 years)(113). Waist size, specifically, waist circumference (WC), may better encapsulate differences in distribution of fat with respect to later clinically relevant metabolic outcomes in developing black

and white adolescent girls. Racial differences in any long-term effects of early adolescent waist circumference, a simple anthropometric measure of central adiposity, in black and white girls on their later lipid levels, a marker that may be a prelude of CMR, is not well understood.

1.7 Racial and Maturation Differences in Cardiometabolic Risk

Physical maturation(108,114–116) and the composite of physical, hormonal, and behavioral changes during puberty may impact subsequent cardiometabolic risk differently in blacks and while during adolescence. For example, black girls tend to go through puberty earlier than white girls, and their earlier early age at menarche(115) has been associated with insulin resistance(117) and elevated blood pressure(118). Early menarche is associated with insulin resistance, independent of body composition and age: this observation could reflect changes in skeletal muscle tissue during adolescence rather than central adiposity. A study in the Fels Longitudinal cohort (119)demonstrated that girls with early menarche tended to retain hyperinsulinemia or IR throughout puberty, without normal recovery of IR after the pubertal transition. Blood pressure, glucose, lipids, and anthropometric measures of adiposity are all biological risk factors measured in NGHS. Racial

disparities in CMR outcomes such as lipid levels and insulin resistance have been identified in other adolescent populations(108), as well as in NGHS(113,117,118,120–124). Mortality rates due to cardiovascular disease are higher in black than in white women; this is thought to be due in part to the higher prevalence and earlier onset(125) of hypertension among black women(126). The racial disparity in cardiometabolic risk may be due to racial differences in body fat or composition as well as other early life behavioral and physical predictors(127).

1.8 Connections between obesity, dyslipidemia, and cardiovascular disease

Obese children are more likely to be at risk for subsequent heart disease than non-obese children. Adolescent obesity is correlated with other cardiometabolic risk factors, such as risk of later elevated blood pressure, in many studies, including the Bogalusa Heart Study, where overweight during childhood that persisted into adulthood was related to adverse risk levels in both blood pressure and lipids among adults(128,129).

Among adolescent girls and young adult women, a few studies hypothesized that timing of menarche might be an upstream instigator of a

pathway associated with greater and persistent weight gain and increased obesity(130–132). The Cardiovascular Risk in Young Finns study, with 27 years of follow up, integrated key potentially mechanistically related cardiometabolic risk factors such as serum lipids, blood pressure, and BMI – for the purpose of better understanding the effects of obesity on the architecture of the cardiovascular system and structure-to-function relationship. Obesity in youths was significantly associated with increased carotid artery intima-media thickness and decreased carotid artery elasticity in adulthood(133), a finding that is associated with risk of both high blood pressure and subsequent cardiovascular disease.

While body fat has been shown to be associated with blood pressure and serum lipids in a biracial population of youth(5), more supporting data concerning the ability of early body composition to predict dyslipidemia is still needed. It has not been determined if early adolescent, pre-pubertal waist size predicts dyslipidemia. Since maturation affects body composition, understanding the role of maturation in body fat related dyslipidemia could add important insights to our understanding of causes of dyslipidemia.

In this dissertation, I will compare anthropometric measures of body fat at pre-and post-menarche baseline time points to better understand racial differences in these simple indicators of body fat as predictors of dyslipidemia during late adolescence. I will compare waist size with other measurable body composition predictors, such as body mass index, percent body fat, and waist-to-hip ratio to determine which of these early measures of body composition best predicts lipid-related outcomes in late adolescence.

1.9 Addressing a Pressing Problem – New Approaches to Primary Cardiovascular Risk Prevention with Prospective Cohorts

To address current complex social environments, the risk factors that comprise the context of adult chronic diseases need to be even more comprehensive. Disparities in risk associated with race and socioeconomic status, and family-based factors in the home, including those affecting the mother's health are interrelated and must be considered as important factors shaping a child's health and wellbeing.

The ability to track adiposity and the development of associated cardiovascular disease risk factors such as dyslipidemia in children and

adolescents, over time, in a large cohort like NGHS is an important value of this dissertation work. Here, I will examine predictors of cardiometabolic risk that include a broad combination of genetic, physical, psychosocial, lifestyle and environmental factors that work together, often through action on obesity and weight-related actors, to increase risk of adult chronic disease. *In this study, we aim to identify early predictors of dyslipidemia and obesity that, if screened for in adolescence, may help shrink the health disparities gap in mortality due to cardiovascular causes in adult women.*

1.10 Overall Objectives of the Dissertation

Children of different races and socioeconomic statuses experience disparities in obesity risk(2,13–15) and must continue to be a focus of nutrition research to inform the targeted interventions that best serve these at-risk populations(134). Our study in NGHS provides a unique opportunity to integrate a wealth of data on 1) psychosocial predictors in mothers and their daughters with 2) detailed diet records, and 3) physical and biological measures of risk. NGHS is a large cohort of 2,379 9-10 year old girls followed prospectively for 10 years (70).

This study includes a combination of important, but understudied, predictors of child obesity and cardiometabolic risk in black and white girls of differing socioeconomic statuses. Depressed mothers are often unable to buffer family stressors and to supply a supportive child-adult relationship that is involved and responsive. This lack of a mother's capacity to guide the healthy development of eating behaviors in their children(58,135) during family meals(22,25,73,136) may become a source of toxic stress, thereby promoting the risk of obesity and metabolic disorders. This research could add new evidence to identify targets not previously studied in a large, racially diverse population.

1.11 Specific Aims

Specific Aim 1:

To compare the ability of early-adolescent anthropometric measures of body fat (i.e., BMI, WC, WHR, %body fat from BIA) to predict later blood lipid levels in black and white girls in later adolescence.

Specific Aim 2:

To compare the efficacy of pre- and -post-menarche BMI as a predictor of lipid levels in late adolescence in young black and white girls

Specific Aim 3:

To estimate the effects of maternal depressive symptoms, on daughter's change in BMI from ages 9-10 to 18-20 years of age as well as level of late adolescent BMI and further, to determine whether these effects are explained by factors such as the child's self-worth or depressive symptoms.

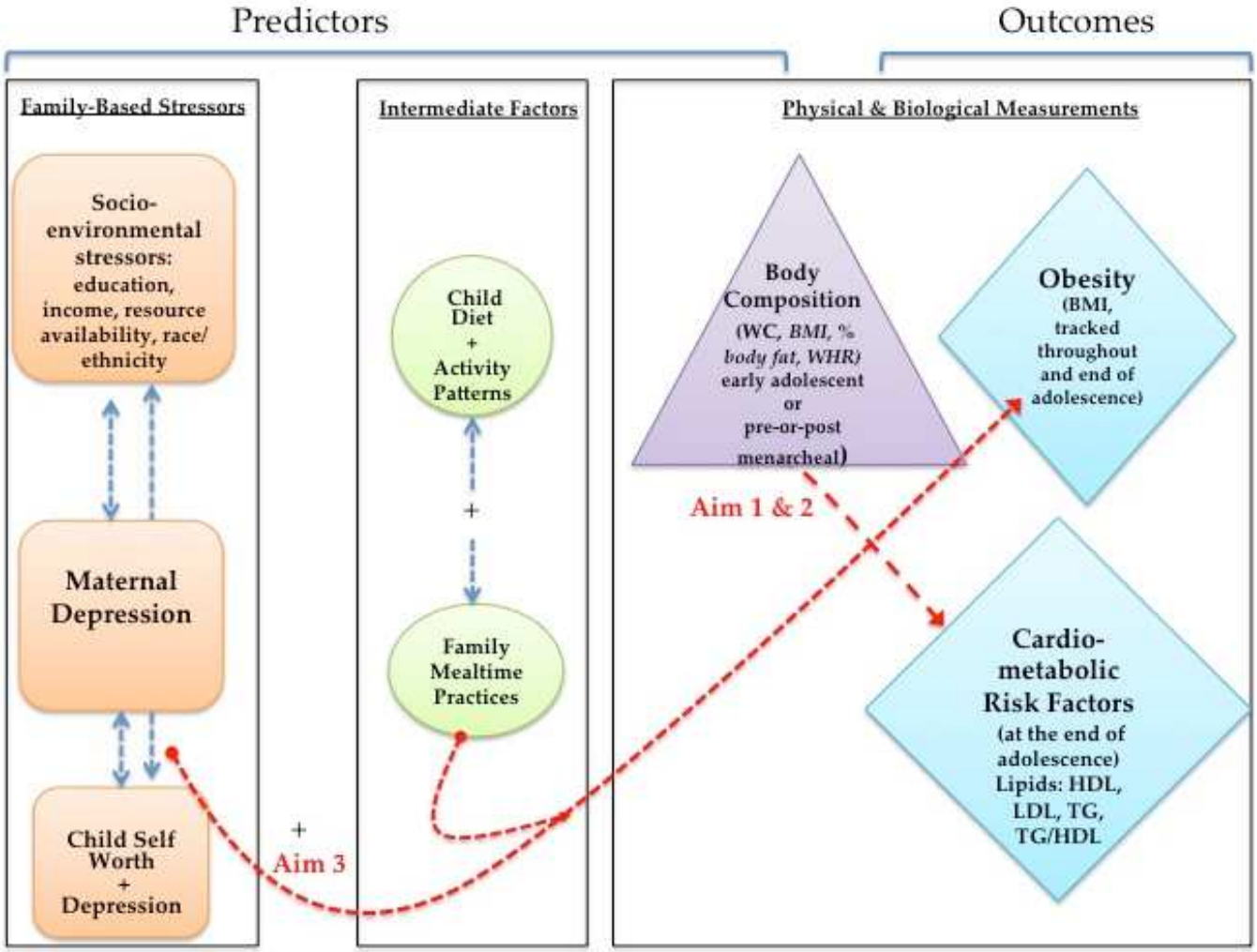


Figure 1.0 Schematic of Aims

1.12 Overview of Methods

We performed a secondary data analysis within the National Heart Lung and Blood Institute's (NHLBI) NGHS cohort. NGHS is a bi-racial prospective cohort of 2,379 black and white girls enrolled in a multicenter study at ages 9-10 years in 1987-1988 and followed longitudinally for ten years. Parents or guardians were required to identify with the same race as the child to be eligible. The goal of the original study was to investigate the development of obesity in black and white girls during adolescence as well as the environmental, psychosocial, and cardiovascular disease risk factors that may explain the higher risk of cardiovascular disease in black women. Demographic, anthropometric, dietary intake and eating patterns, physical activity records and patterns, psychosocial measures, beliefs and attitudes about certain aspects of health, body satisfaction and family influences were measured and detailed methods for collection of these variables are described in detail elsewhere(116,124,137). Statistical analyses and modeling use the SAS 9.4 package. In our two main aims, we employ multivariable modeling, including general linear models, mixed linear models, and logistic models, to address questions surrounding two of the four primary cardiometabolic risk factors – dyslipidemia and obesity.

CHAPTER TWO: A comparison of the ability of early adolescent body measures to predict later blood lipids in later adolescence

2.0 Abstract

Adult chronic diseases have their roots in childhood. Our study sought to understand how useful measures of early adolescent waist circumference (WC), body mass index (BMI), waist to hip ratio (WHR), and percent body fat from BIA (%BF) are in predicting levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides (TG) in black and white girls in late adolescence. While BMI has mainly been used in clinical settings to estimate a child's propensity for obesity and associated metabolic risk, the limitations of BMI are apparent. The National Heart Lung and Blood Institute's Growth and Health Study (NGHS) was used to evaluate effects of early adolescent waist size and other anthropometric measures of body fatness in black and white girls on lipid levels in later adolescence. We used analysis of covariance to attempt to answer the question of how useful anthropometric body composition measures are at ages 9-10 in predicting lipid levels in late adolescent years, while controlling for confounding by demographic and behavioral risk factors. Black girls had substantially lower pre-adolescent %BF (23.6% vs. 26.4%) than whites,

but gained fat more rapidly (34.7% vs. 14.0% increases), exceeding whites in %BF by late adolescence. WC was a stronger predictor of subsequent LDL levels than other measures of body fat (LDL of Q5-Q1 of WC: 29.5 mg/dL in whites; Q5-Q1: 17.9 mg/dL in blacks). Regardless of race, BMI and WC predicted increases in LDL, TG, and TG/HDL (triglyceride to HDL ratio), and decreases in HDL. Early adolescent WC and BMI were better predictors of HDL in black girls (R^2=0.06) compared to in white girls (R^2=0.04) in late adolescence. In particular, a higher WC in both white and black girls was associated with lower HDL cholesterol ($p<0.0001$). While BMI and WC were stronger predictors of later lipids compared to %BF and WHR, in black girls, %BF was a better predictor of later LDL and TG, and WHR was also a better predictor of later HDL compared to in white girls. Since HDL is a marker for metabolic risk, WC could be useful to identify early adolescent girls who may be at elevated risk for later chronic disease; this information could potentially help prevent obesity-related cardiometabolic risk due to dyslipidemia amongst white and black girls. These results suggest that WC and BMI are simple anthropometric measures of body composition in early adolescent girls that may be useful to identify girls who are at risk for unhealthy lipid levels by the time of later adolescence.

2.1 Background

Childhood obesity is an epidemic in the United States(1,2) as well as worldwide and the costs are great(3,4); every year, it puts children on a trajectory leading to chronic metabolic diseases(5,7–9). Waist circumference is an important risk factor for elevated lipids in adults(138–141). A number of recent studies have compared various measures of adiposity as predictors of CMR, with each focusing on different populations, length of study, and selected measures of adiposity, however there are still important questions to ask to better understand if early adolescent adiposity may be a useful predictor of later lipid levels, and if there are differences with respect to race. How well early adolescent (in 9-11 year olds) WC, a simple anthropometric measure of central adiposity, functions in black and white girls to predict higher levels of lipids in later adolescence - as one example of subsequent CMR - is an area that requires further research to support any updates to clinical guidelines for early assessment of later CMR.

A number of studies in children of various backgrounds and ages in childhood and adolescence have compared measures of adiposity in their ability to predict different individual or clusters of CMR. In 2016, Sardinha et al.(48) compared BMI, WC, and waist-to-height ratio (WHtR) as measures of adiposity

for predicting clusters of CMR (including increased triglycerides, high-density lipoprotein, systolic and diastolic blood pressure, and insulin resistance) in children and adolescents. The authors found that the magnitude of associations were similar across measures for this cohort of 8-17 year old girls and boys, but precision to classify increases in risk was low. In contrast, Bluher et al.(142) found that WHtR was not better than BMI or WC at predicting CMR in the former. Similarly, Jensen et al.(143) determined that WHtR was not a better predictor of nutritional status. One study also compared WC, BMI and WHtR, but did so in a small group of overweight/obese children aged 3-5 years old and similarly concluded that WHtR was not superior to WC or BMI in correlation with CMR, and do not support its use in young children. This is not clear, however as McCarthy et al.(144) found that WHtR was a better measure of childhood morbidity among a survey of British children compared to BMI, and Savva et al.(145) determined that WHtR was better than BMI at cross-sectional prediction of lipid and lipoprotein pathological values among Greek-Cypriot children who were 11-years old. In a cross-sectional study pre-puberty, Maffeis et al. (146) compared WC with either triceps and subscapular skinfolds to explore the relationship between these anthropometrics and lipids, among other CMR, and found that although WC and skinfolds can help identify adverse blood lipid

profiles, WC is preferable as an easy to measure and more easily reproducible way to identify clinically relevant intra-abdominal fat in children than skinfolds.

Body mass index (BMI) has been used in pediatric populations to track risk for overweight and obesity. Prior work in NGHS showed that girls who were overweight (at 9 years) were 11-30 times more likely to be obese in adulthood (at 21-23 years)(113). While BMI has mainly been used in clinical settings to estimate a child's propensity for obesity and associated metabolic risk, the limitations of BMI are apparent. BMI does not capture sources of body composition, particularly depots of visceral adipose tissue that are highly associated with metabolic disease(109). With respect to clinically relevant metabolic outcomes in developing adolescent girls, waist circumference (WC) may add some information about distribution of fat. The utility of WC as a predictor of health risk in adults and youths has been previously shown. Waist size has been proven useful to highlight disparities between black and white adults (112,147). WC was also a useful body composition marker of cardiometabolic risk factors in some smaller studies in youths, including an understudied group of minority youths (ages 2-19 years) from Central and South America and the Caribbean (110), and of Scottish boys (14-16 years)(111).

Freedman et al. performed a cross-sectional, community-based analysis of Bogalusa Heart Study subjects, and found that WC, as a surrogate of body fat patterning, was helpful to identify children likely to have higher LDL, and lower HDL concentrations(148), suggesting that WC could be as useful as BMI because it is a good predictor of future health risks, and can be easily measured and understood. This is still an area without universal agreement, as another study(149) disagrees with the necessity of WC, after comparing the Bogalusa Heart Study age-and-sex-specific waist circumference cutoffs for children and adolescents (150) to the International Obesity Task Force (IOTF) BMI cutoffs(151) for predicting cardiovascular risk clustering. They hold BMI as sufficient to represent body composition as a determinant of cardiovascular disease risk clustering.

To evaluate the value of various anthropometric body composition measures as predictors of later adolescent lipid levels, we propose that it may be important in our study to examine racial differences, and to investigate the potential contribution of pubertal maturation(108,114–116) in the relationship between early adolescent adiposity and later lipid levels. There are known racial differences in central adiposity between white and black girls in NGHS(124),

where black girls tended to have significantly higher WC than white girls, and these increases occurred at a quicker rate, even after adjusting for age at menarche. While rates of change in individual lipid levels exhibit differences based on overweight and non-overweight status of NGHS girls between ages 9-12 and after age 12, early adiposity also appears to identify what may be non-overweight-related lipid differences due to race (113). Regardless of overweight status, black girls were less likely than white girls to have unhealthful HDL or TG, but there were no statistically significant racial differences in LDL(113). That same study suggested that maturation may also explain some of the variation in unhealthy lipid levels: maturation may impact lipids above and beyond age alone in association with overweight; adding in maturation tended to result in tighter confidence intervals. Accounting for maturation, unhealthful LDL became significantly associated with overweight. Another study by Bluher et al.(142) of obese girls and boys of German/Austrian/Swiss descent, ages 11-18, observed that the patterns of body composition associated with CMR changed throughout pubertal development, with strongest associations for those individuals who were already pubertal. In the same study, BMI and WC were correlated, and lipids were more strongly correlated with WC compared to BMI or WHtR, but more so in boys than in girls.

The first objective of this study is to assess the utility of BMI, WC, WHR, and %BF - simple continuous, anthropometric measures of body fat - collected at ages 9-10 years – for predicting later adolescent lipid levels at ages 17-20. Secondly, our next objective was to study racial differences in the prediction of lipid levels in later adolescence using these same measures of adiposity in 9-10 year-old black or white girls. Of particular interest was the question of whether WC, as an indicator of fat patterning and distribution in young girls would be a better predictor of later lipid levels than measures of BMI at similar times.

2.2 Methods

2.2.1 Study Population

Data from the National Heart Lung and Blood Institute's Growth and Health Study (NGHS) was used for this study. Study participants in NGHS were recruited from three separate geographic areas to minimize the likelihood of biased results due to regional differences and to allow for comparison across socioeconomic backgrounds. Subjects were recruited from census tracts that had approximately equal black and white residents and the least disparity in education and income(122). Children were enrolled from three clinical centers:

the University of Cincinnati/ Cincinnati Children's Hospital Medical Center in Ohio, Westat, Inc./Group Health Association in Rockville, Maryland, and University of California at Berkeley, in Berkeley, CA and were followed prospectively for 10 years. Berkeley and Cincinnati girls were recruited from public and parochial schools, and those from Westat were recruited from a health maintenance organization. The criteria for the selection of subjects and broad exclusion criteria from the original cohort have been previously described in detail(116–118). Research protocols were reviewed and approved by the NHLBI's Institutional Review Board. Measurements of the exposures, outcomes, and potential co-variables in our study in NGHS were evaluated according to study protocol at annual exams by examiners who were certified, monitored, and trained to use the NGHS protocol.

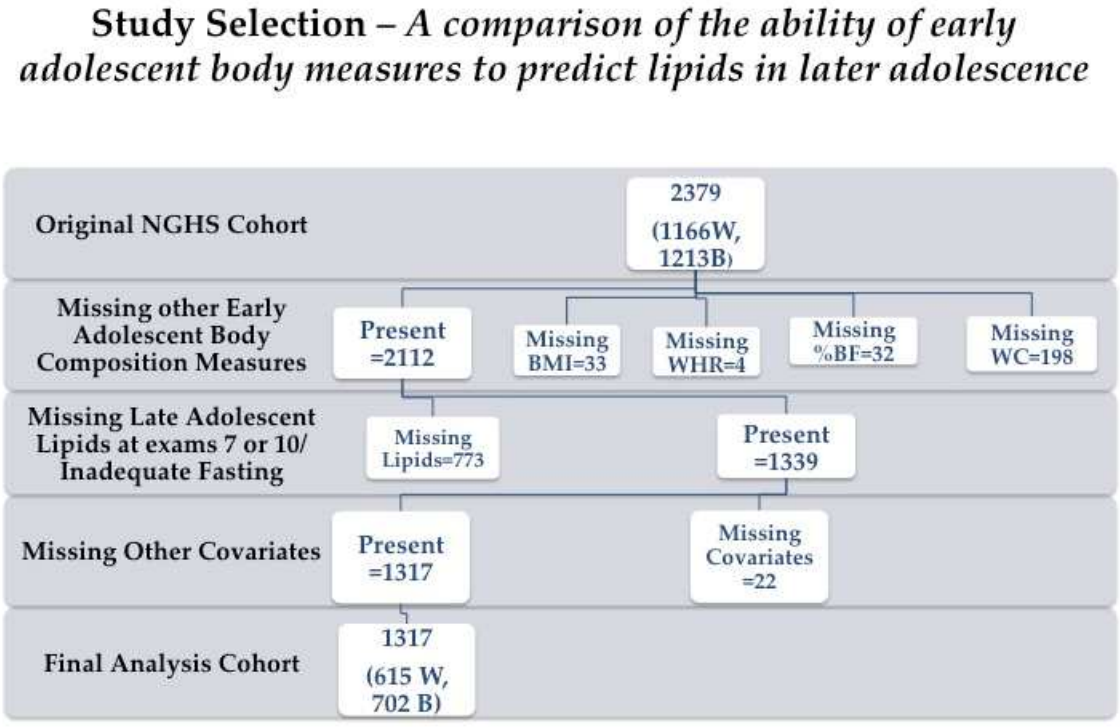
Inclusion and Exclusion Criteria

Eligibility Criteria: In brief, girls eligible for recruitment in NGHS had to meet the following criteria (a) within two weeks of age 9 or 10 at the time of the first clinic visit(120); (b) be self-defined as black or white and come from racially concordant Caucasian or African American households; and c) parents had to

complete a household demographic form, give parental consent and the child also gave assent for participation in the study.

Study Sample Selection Criteria: For the analyses examining anthropometric predictors of late adolescent lipid levels, we included girls with complete data (n=615, white girls; n=702, black girls) for all anthropometric measures of early adolescent body composition taken from ages 9-10 (BMI, WHR, %BF by bioelectric impedance analysis [BIA], and WC), confounding variables retained in the final models (baseline height at ages 9-10, menarche age, SES, physical activity [averaged from ages 9-17]), and follow-up lipid levels (LDL, HDL, and TG) at 17-20 years of age. We compared the subjects who were included with those who were excluded and there were no large differences between the two groups. The included subjects had slightly higher baseline adiposity than excluded subjects: mean baseline BMI (18.9 ± 3.9 vs. 18.6 ± 3.9 kg/m^2), %BF (24.4 ± 7.12 vs. 24.52 ± 7.1 %), WC (65.2 ± 9.3 vs. 65.21 ± 9.2 cm.). The opposite was true for activity levels (19.7 ± 9.8 vs. 21.0 ± 11.4 METs), which were slightly lower for included subjects.

Figure 2.1 – Study Sample Selection Tree



2.2.2 Exposure Variables

Anthropometric Measures of Body Composition

Height was measured to the nearest 0.1 centimeter with socks using custom portable stadiometers, and weight to the nearest kilogram using an electronic Health-O-Meter scale, in duplicate. A third measurement was taken if the two measures differed by more than 0.3 kg for weight or 0.5 cm for height. These were obtained for both mothers and their children.

Anthropometric body composition measures that we used as exposures in our analyses were: BMI, WC, and %BF by BIA and WHR from the earliest obtained measure available between ages 9-10. For BMI and %BF by BIA, the adiposity measure was obtained for ages 9-10. The WC and WHR adiposity measures also included girls who were age 11: 1,058 girls had waist available at ages 9-10, and data substitution was used to include an additional 1,123 girls for whom the earliest available measure of waist was at age 11. BMI was calculated from annual measurements as weight in kilograms divided by height in meters squared. WC was measured in duplicate in centimeters at the minimum waist(123,152), against the skin beginning with the second NGHS visit (girls were between 9-11 years old). Hip circumference was measured in centimeters as the maximum circumference below the waist, also measured in duplicate. WHR was calculated as the ratio of WC to hip circumference measurements.

Percent body fat was estimated using previously validated race specific equations for predicting fat-free mass (FFM). %BF was calculated as follows: %BF = Total Body Fat (TBF)/weight x 100, where TBF = weight – FFM. To determine FFM for those equations, separate race specific equations were derived from predictive models of FFM based on dual energy x-ray anthropometry (DXA) in a

sample of 65 white and 61 black girls, 6-17 years of age(153). Bioelectrical impedance analysis was used to obtain resistance and reactance measures to the nearest ohm by tetrapolar placement of electrodes on the right side of the body(152). Then, resistance and reactance were used in equations designed for the NGHS cohort with ethnicity-specific coefficients to compute percent body fat. The equation for prediction of FFM in black girls used height^2/resistance, weight, and reactance as predictor variables. The equation for prediction of FFM in black girls was the sum of the [intercept] + [resistance parameter] x [height^2/resistance] + [reactance parameter] x [reactance] + [weight parameter] x [weight].

Equation for FFM for Black Girls:

FFM=-8.78 + 0.78*((HEIGHT*HEIGHT)/RESISTANCE) + 0.1*REACTANCE + 0.18*WEIGHT

For white girls, the equation for prediction of FFM used height^2/resistance, weight, and tricep skinfold thickness as predictor variables. The equation for prediction of FFM in white girls summed the [intercept] + [resistance parameter] x [height^2/resistance] + [triceps skinfold parameter] x [triceps skinfold] + [weight parameter] x [weight].

Equation for FFM for White Girls:

FFM=1.07 + 0.37*((HEIGHT*HEIGHT)/RESISTANCE) + -0.17*TRICEPS SKINFOLD + 0.47*WEIGHT

These race specific coefficients were cross-validated with a separate sample of 1 African American and 20 Caucasian girls from the National Institute of Child Health and Human Development, ages 6 to 17 using the Prediction of Sum of Squares statistic(153). Morrison et al. (153) found that there was good agreement between DXA and the prediction equations for girls of each race. Coefficients of variations indicated that equations predicting FFM for white girls offered a slightly better fit than those for black girls.

2.2.3 Outcome Variables

In our study, we evaluated fasting LDL, HDL, and TG. Lipids were analyzed at Johns Hopkins Lipid Laboratory at exams 1,3,5,7, and 10. Lipid outcomes in our analysis included an average of all available lipids when the girls were 17-20 years of age. In NGHS, LDL was calculated using the modified Friedewald equation which estimated LDL-C by dividing TG value by 6.5 to

provide a better estimate of LDL-C in children(154). For LDL, TC, and TG, 494 girls who reported fasting 8 hours or less were excluded(155).

2.2.4 Potential Confounding Variables

Demographic Factors

Age was the exact age calculated based on the child's date of birth. Race/ethnicity was self-declared and collected at study entry. Categories of SES were created by combining data on income and education as follows: (a) low - household income < $10,000, regardless of education level or household income from $10,000 - <$20,000 and education level of high school or less; (b) moderate - household income $10,000 - <$20,000, household income $20,000 - <$40,000, regardless of education, or household income $40,000 or more with only a high school education or less, and (c) high - more than a high school education and an income of $40,000 or more.

Dietary Variables

A wide range of dietary variables was measured and available for use. Diet was assessed in 8 of the 10 total yearly exam visits (at years 1,2,3,4,5,7,8, and 10) using a 3-day food diary including two weekdays and one weekend day. To

complete the diaries, girls were given instructions by registered dieticians and provided with a set of measuring cups, spoons, and a ruler along with a binder of illustrated instructions on how to record portion sizes for their food intake using household measures. Three-day food records were used to record dietary intake, and after these were completed, nutritionists interviewed the girls to verify the entries.

Food records from 2,147 (86% of the black girls, and 95% of the white girls) out of 2,379 girls enrolled in NGHS at baseline were received. To analyze the nutrient content reflected in these records, they were entered into the University of Minnesota's Nutrition Data System (NDS)(156). The NDS estimates daily intake of nutrients based on these food records. Servings of USDA-defined food groups (157)were derived from the NDS output by linking ingredient codes with food codes from the USDA's "MyPyramid Equivalents Database". Together, this provided each subject's nutrient intake along with intakes in all USDA food groups and subgroups, including but not limited to total energy, carbohydrates, protein, fat, dairy, fruit and vegetable, whole grain, and fiber. Average intakes from ages 9 to 17 were used in our analysis.

Physical Activity and Television

Physical activity patterns were assessed during administered structured interviews in study years 1,3, and 5 and then self-administered for years 7-10 where activity was measured by self-report in a Habitual Activity Questionnaire (HAQ) (adapted from Ku et al.(158)) that described exercise patterns of the last year(159). Standardization and optimization of data collection on physical activity in NGHS was established during year 7 of NGHS at the University of Pittsburgh's Physical Activity Resource Unit. Activity from physical activity classes, sports in the school year or summer, summer physical activity, and activity in the rest of the year were summed for an overall physical activity score.

The HAQ score in MET-times per week in each of these categories was computed by multiplying the MET (metabolic equivalent, the ratio of metabolic rate during a specific physical activity to a reference metabolic rate, where 1 MET = 3.5 ml 0_2 kg^{-1} min^{-1} in MET/min/day) scores for activities by weekly frequency, and a fraction that reflected if the activity was completed during "most", "half" or a "small part" of the designated time of the year from the activity diary(160,161). These weekly summary scores were modified from those used in

adult studies to reflect energy expenditure commonly associated with those activities for a given age and gender over the whole past year.

Television (TV) or video hours in half hour increments were collected in two ways: 1) hours usually watched were collected using a reference directory of specific programs (study years 1,3,5) updated annually, and 2) by report of TV hours usually watched (study years 6-10) during the morning, afternoon, and nighttime hours of a typical week (161). In a methodological test in the first exam, a subset of participants was asked about hours of TV usually watched using listing of programs, and this was compared with the their response to a weekly estimate of the number of hours of TV, movies, or videos that they watched that week. Data captured from programs watched was found to be more accurate, and the first method was used in earlier exams. Average physical activity METs and TV or video watching hours per week over ages 9-17 was used in our analysis.

Sexual Maturation

Maturation was ascertained using age at menarche (113) based on questions asked of the girls annually, and also assessed by trained nurses based

on indexes of pubic hair distribution and areolar development. Trained nurses used modified Tanner staging principles from criteria developed by Garn and Falkner(162) that classified subjects into four maturational stages: 1) pre-pubertal (stage 1 of either areolar or pubic hair development, pre-menarcheal), 2) pubertal (pre-menarcheal and stage 2 or greater of areolar or pubic hair development), 3) <2 years post-menarche, or 4) >2 years post-menarche(124).

Maternal Factors

Parents provided data at study years 1,3,5, and 7. Biological mother's BMI was collected, at study years 1,3,5 and 7. The first available of these was selected as the mother's BMI in our analyses of the relationship between early factors on later child lipids. Mother's age at first period was ascertained by questionnaire at study years 1 and 3.

2.2.5 Statistical Analysis

Baseline Quintiles of Anthropometry Data

Continuous early adolescent adiposity measures (ages 9-10 years for BMI and %BF; ages 9-11 for WC and WHR) for the overall study population (blacks and whites together) were divided into quintiles at baseline (Q1, Q2, Q3, Q4, Q5).

For these analyses, we did not use z-scores since these are not available for all measures of anthropometry and our goal was to compare these measures. Therefore, we chose to use quintiles for each of the measures to categorize the distributions of BMI, WC, %BF, and WHR in a consistent way. This also allowed us to evaluate whether any non-linear effects (e.g., threshold effects) existed for these measures of body composition and later lipids. Dividing the study population into quintiles better enabled us to capture and show monotonic relationships and trends from the lowest to highest ends of the distribution of each anthropometric measure of body composition. For the purposes of these analyses, using overall quintiles instead of race-specific quintiles was deliberate: it allowed us to compare the same group of girls who were in the each quintile across measures of adiposity, using the same cutoff values for black and white girls.

Descriptive Analyses

We began by exploring trends in body fat over time using the different anthropometric measures of interest and explored the frequency distributions of other variables of interest. To determine the stability of BMI, WC, and %BF throughout adolescence, we compared the classification of girls into quintiles of

body fat at ages 9-10 years with quintiles at the end of adolescence. For example, we ascertained the percent of girls who were in Q1 at 9-10 years of age who remained in that quintile at 17-20 years.

Comparison of anthropometric body composition measures as predictors of later lipid levels

Our objectives were to assess the utility of BMI, WC, WHR, and %BF - simple continuous, anthropometric measures of body fat - collected at ages 9-10 years – to predict later adolescent lipid levels at ages 17-20, and to compare the ability of each of these measures to predict late adolescent lipid levels in black and white girls. We examined a number of variables as potential confounders, including age, baseline height; age at menarche; average hours/day of TV/Video at ages 9-17 years, average physical activity, total cups of dairy, total cups of fruits and vegetables, percent of energy from total fat, dietary fiber, and protein. Many of these factors were predictors of lipid outcomes but most were not confounders. Only those factors found to be confounders of at least one of the anthropometry-lipid relationships were retained in the final models. Potential confounders that changed the effect estimate by more than 10% were considered confounders. We created one final ANCOVA (analysis of covariance) model for

BMI, WC, WHR, and %BF adjusting for height at ages 9-10, SES, age at menarche, and average physical activity from ages 9-17, and then stratified by race. With models of the LDL outcome, baseline height and menarche were confounders for black girls with BMI, WC, and WHR measures. Baseline height was also a confounder of the WC measure in white girls for LDL. For the HDL outcome: baseline height was a confounder among white girls using either the WC and WHR measures of adiposity, and also in black girls with WHR. Finally, for the TG outcome, baseline height was a confounder among black girls using WC, %BF, and WHR and height and activity were confounders among white girls with early WHR measures. As our descriptive analyses also indicated, many of the black girls reached menarche earlier than white girls, further supporting adjustment for age of menarche in our models.

2.3 Results

Baseline Characteristics

Table 2.1 shows that there were a few racial differences in diet or lifestyle behaviors observable at baseline. On average, black girls were taller than white girls (149.3 ± 8.0 cm vs. 145.6 ± 7.7 cm) and had a higher BMI (19.6 ± 4.3 kg/m^2 vs. 18.1 ± 3.2 kg/m^2). Black girls tended to have lower dairy intakes than white girls.

They were also less physically active, and watched more hours of TV per day on average than white girls (5.8 ± 1.7 hrs/day vs. 3.3 ± 1.6 hrs/day). Black girls also consumed a slightly higher percentage of their energy from fat than white girls (36.4% ± 3.5% vs. 33.7% ± 4.0%), and reached menarche slightly earlier on average (12.0 ± 1.1 yrs, vs 12.7 ± 1.2 yrs). 30% of black girls were from families of low SES compared with 13.6% of whites (Table 2.2 and Table 2.3).

Tables 2.2 (white girls) and 2.3 (black girls) displays the descriptive baseline characteristics of adolescent girls by quintile of BMI in early adolescence (ages 9-10), stratifying by race. Many fewer white girls were in the highest body fat quintile compared with blacks. At baseline, black girls already had a waist circumference in race-specific quintile 5 (Q5) of 80.0 ± 7.7 cm, which was also greater than WC in white girls in race-specific Q5 (77.6 ± 7.1). Among either black or white girls, age of menarche tended to decrease linearly as body fat increased.

Table 2.1 Descriptive characteristics of all subjects at ages 9-10

Subject Characteristics	Whites (n=615)	Blacks (n=702)
	(mean ± s.d.)	
Age (yrs)[1]	10.2 ± 0.3	10.3 ± 0.3
Height (cm)[1]	145.6 ± 7.7	149.3 ± 8.0
Age at menarche (yrs)	12.7 ± 1.2	12.0 ± 1.1
TV/Video (hrs/day)[2]	3.3 ± 1.6	5.8 ± 1.7
Physical Activity (METS)[3]	22.4 ± 10.4	17.3 ± 8.6
Dairy (total cups)[2,4]	2.0 ± 0.8	1.4 ± 0.5
Fruits &Veg (total cups)[2,4]	2.0 ± 0.8	1.9 ± 0.9
% Energy from Total Fat[2]	33.7 ± 4.0	36.4 ± 3.5
Dietary Fiber[2]	12.0 ± 3.2	11.2 ± 3.2
BMI (kg/m^2)[1]	18.1 ± 3.2	19.6 ± 4.3
%Body Fat [1]	25.7 ± 5.0	23.5 ± 8.4
Waist Circumference (cm)[1]	63.3 ± 8.0	67.0 ± 10.0
LDL (mg/dL, fasting)[1]	104.9 ± 27.2	105.1 ± 28.7
HDL (mg/dL)[1]	53.0 ± 11.4	55.8 ± 13.3
Triglycerides (mg/dL, fasting)[1]	79.0 ± 38.1	71.3 ± 32.1
[1]Baseline ages 9-10 [2]Average from ages 9-17 [3]MET-Metabolic equivalent per week [4]Total cup equivalents		

Table 2.2. Descriptive characteristics of white girls by quintile of body mass index at ages 9-10

BMI Quintiles of White Girls					
Subject Characteristics	**Quintile 1 (n=145)**	**Quintile 2 (n=139)**	**Quintile 3 (n=133)**	**Quintile 4 (n=118)**	**Quintile 5 (n=81)**
	(column %)				
SES[1]					
Low	**6.2%**	**7.2%**	**13.5%**	**5.9%**	**13.6%**
Moderate	**39.3%**	**38.1%**	**37.6%**	**43.2%**	**50.6%**
High	**54.5%**	**54.7%**	**48.9%**	**50.9%**	**35.8%**
	(mean ± s.d.)				
Age (yrs)[2]	**10.2 ± 0.3**	**10.2 ± 0.3**	**10.2 ± 0.4**	**10.2 ± 0.3**	**10.2 ± 0.3**
Height (cm)[2]	**142.5 ± 6.9**	**144.1 ± 7.3**	**145.9 ± 7.2**	**147.7 ± 7.7**	**149.9 ± 7.6**
Age at menarche (yrs)	**13.3 ± 1.2**	**12.9 ± 1.1**	**12.4 ± 1.2**	**12.3 ± 1.3**	**12.1 ±1.0**
TV/Video (hrs/day)[3]	**3.0 ± 1.5**	**3.1 ± 1.6**	**3.2 ± 1.6**	**3.5 ± 1.5**	**3.8 ± 1.5**
Physical Activity (METS)[4]	**21.4 ± 10.1**	**23.8 ± 11.1**	**23.6 ± 9.9**	**22.6 ± 11.2**	**19.8 ± 8.5**
Dairy (total cups)[3,5]	**2.0 ± 0.8**	**2.0 ± 0.8**	**2.0 ± 0.8**	**2.0 ± 0.8**	**1.9 ± 0.7**
Fruits & Veg (total cups)[3,5]	**2.0 ± 0.7**	**2.1 ± 0.9**	**2.0 ± 0.9**	**2.0 ± 0.8**	**1.9 ± 0.8**
% Energy from Total Fat[3]	**33.6 ± 3.4**	**33.4 ± 4.1**	**33.5 ± 4.1**	**33.8 ± 4.0**	**34.5 ± 4.4**

Dietary Fiber[3]	**12.1 ± 3.2**	**12.3 ± 3.3**	**11.8 ± 3.0**	**11.9 ± 3.3**	**11.5 ± 3.2**
BMI (kg/m^2)[2]	**14.8 ± 0.7**	**16.4 ± 0.4**	**18.0 ± 0.5**	**20.0 ± 0.8**	**24.4 ± 2.6**
%Body Fat[2]	**21.2 ± 3.0**	**23.5 ± 2.9**	**25.9 ± 3.4**	**28.5 ± 3.8**	**33.1 ± 2.8**
Waist Circumference (cm)	**55.8 ± 2.7**	**59.3 ± 3.0**	**63.1 ± 3.2**	**67.7 ± 4.5**	**77.6 ± 7.1**
LDL (mg/dL)[2]	**101.3 ± 22.2**	**106.3 ± 28.7**	**99.6 ± 25.7**	**107.6 ± 28.3**	**113.2 ± 29.5**
HDL (mg/dL)[2]	**56.3 ± 10.4**	**53.7 ± 11.8**	**54.0 ± 1.0**	**51.4 ± 11.5**	**46.5 ± 10.2**
Triglycerides (mg/dL)[2]	**66.4 ± 26.0**	**80.0 ± 29.7**	**73.3 ± 29.5**	**81.5 ± 34.4**	**106.4 ± 65.5**

[1]Low=income <$20,000 and ≤high school or income <$l0,000; high=income ≥$40,000 and >high school; moderate=those not qualifying as low or high

[2]at baseline ages 9-10

[3]Average from ages 9-17

[4]MET-Metabolic equivalents per week

[5]Total cup equivalents of fruits and vegetables

Table 2.3. Descriptive characteristics of black girls by quintile of body mass index at ages 9-10

BMI Quintiles of Black Girls					
Subject Characteristics	**Quintile 1 (n=119)**	**Quintile 2 (n=125)**	**Quintile 3 (n=131)**	**Quintile 4 (n=146)**	**Quintile 5 (n=183)**
	(column %)				
SES[1]	**36.1%**	**36.0%**	**37.4%**	**28.1%**	**30.1%**
Low	**43.7%**	**40.8%**	**42.0%**	**50.7%**	**42.6%**
Moderate	**20.2%**	**23.2%**	**20.6%**	**21.2%**	**27.3%**
High					
	(mean ± s.d.)				
Age (yrs)[2]	**10.2 ± 0.3**	**10.2 ± 0.3**	**10.2 ± 0.4**	**10.3 ± 0.4**	**10.3 ± 0.3**
Height (cm)[2]	**144.9 ± 7.7**	**147.8 ± 7.5**	**149.0 ± 8.7**	**150.5 ± 7.1**	**152.5 ± 7.0**
Age at menarche (yrs)	**12.6 ± 1.0**	**12.1 ± 1.0**	**12.0 ± 1.1**	**11.8 ± 1.1**	**11.8 ± 1.2**
TV/Video (hrs/day)[3]	**5.6 ± 1.8**	**5.9 ± 1.6**	**5.6 ± 1.8**	**5.8 ± 1.7**	**6.1 ± 1.7**
Physical Activity (METS)[4]	**16.5 ± 7.3**	**16.8 ± 7.6**	**18.1 ± 9.8**	**17.2 ± 8.3**	**17.5 ± 9.5**
Dairy (total cups)[3,5]	**1.4 ± 0.5**	**1.4 ± 0.6**	**1.4 ± 0.5**	**1.4 ± 0.5**	**1.3 ±0.5**
Fruits &Veg (total cups)[3,5]	**2.0 ± 0.7**	**1.9 ± 0.6**	**1.9 ± 0.7**	**1.9 ± 0.7**	**1.8 ± 0.7**
% Energy from Total	**36.3 ± 3.4**	**36.5 ± 3.4**	**36.5 ± 3.3**	**36.4 ± 3.7**	**36.3 ± 3.6**

Fat[3]					
Dietary Fiber[3]	11.5 ± 2.9	11.3 ± 2.9	11.5 ± 3.1	11.3 ± 3.5	10.5 ± 2.6
BMI (kg/m²)[2]	14.8 ± 0.7	16.4 ± 0.4	17.9 ± 0.5	20.1 ± 0.9	25.6 ± 3.1
%Body Fat [2]	15.6 ± 4.4	17.9 ± 4.4	20.0 ± 5.0	25.2 ± 4.8	33.6 ± 5.8
Waist Circumference (cm)[2]	56.5 ± 2.9	60.2 ± 3.0	62.8 ± 3.5	68.6 ± 4.5	80.0 ± 7.7
LDL (mg/dL)[2]	108.9 ± 31.3	98.0 ± 27.4	101.0 ± 30.7	105.5 ± 26.5	109.9 ± 27.0
HDL (mg/dL)[2]	60.9 ± 12.5	57.8 ± 13.6	56.7 ± 13.9	56.5 ± 12.0	50.0 ± 12.1
Triglycerides (mg/dL)[2]	64.6 ± 31.2	65.2 ± 29.6	66.5 ± 23.7	73.1 ± 35.7	81.7 ± 34.0

[1]Low=income <$20,000 and ≤high school or income <$10,000; high=income ≥$40,000 and >high school; moderate=those not qualifying as low or high

[2]at baseline ages 9-10

[3]Average from ages 9-17

[4]MET-Metabolic equivalents per week

[5]Total cup equivalents for fruits and vegetables

Descriptive Results

Figure 2.2 shows the distribution of age at menarche for black and white girls; here, black girls reach menarche slightly earlier than white girls on average. Figure 2.3 tracks BMI over the course of the study from ages 11-21, in two-year intervals according to quintiles of early adolescent waist circumference. BMI increases throughout adolescence in a linear manner in each of the quintiles of early waist circumference. This trend is similar in both whites and blacks. In Q5, among girls who had the highest levels of early waist circumference, the slope of BMI throughout adolescence appears slightly steeper in black girls than in whites. It is also apparent that the maximum WC in older black girls (115 cm) was higher than that seen in white girls (99.25 cm).

Figure 2.2 – Black girls reached menarche in the NGHS Population somewhat earlier than white girls

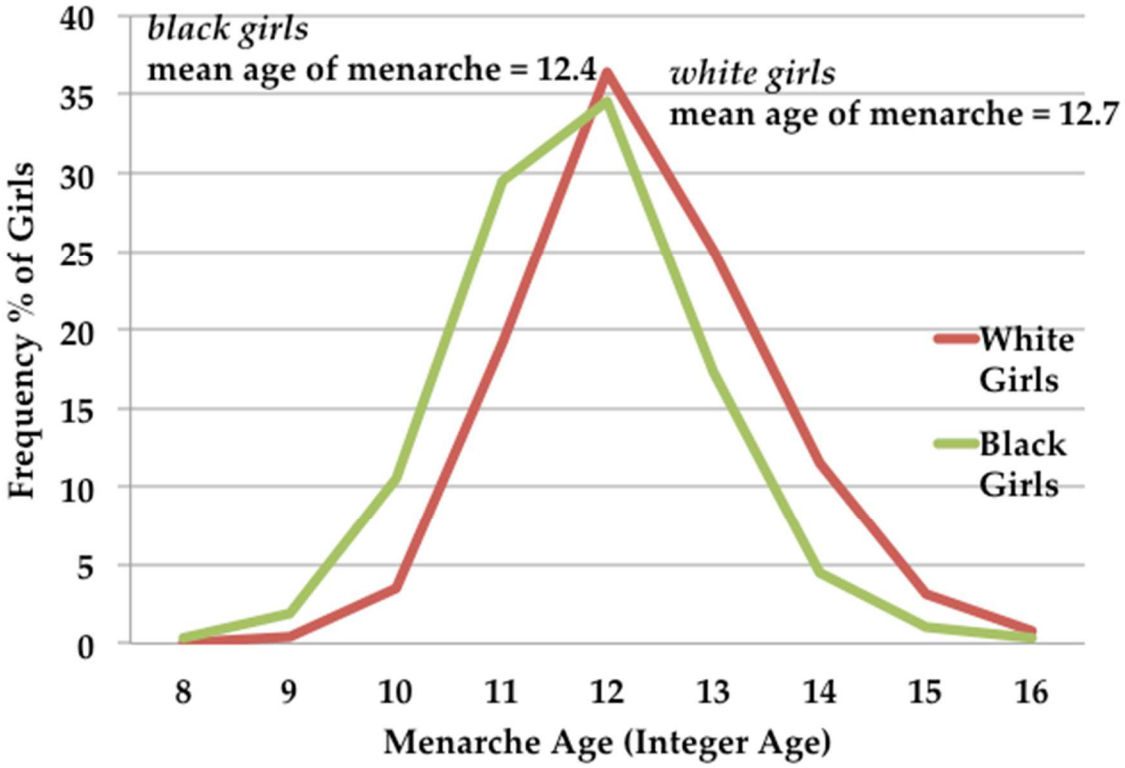
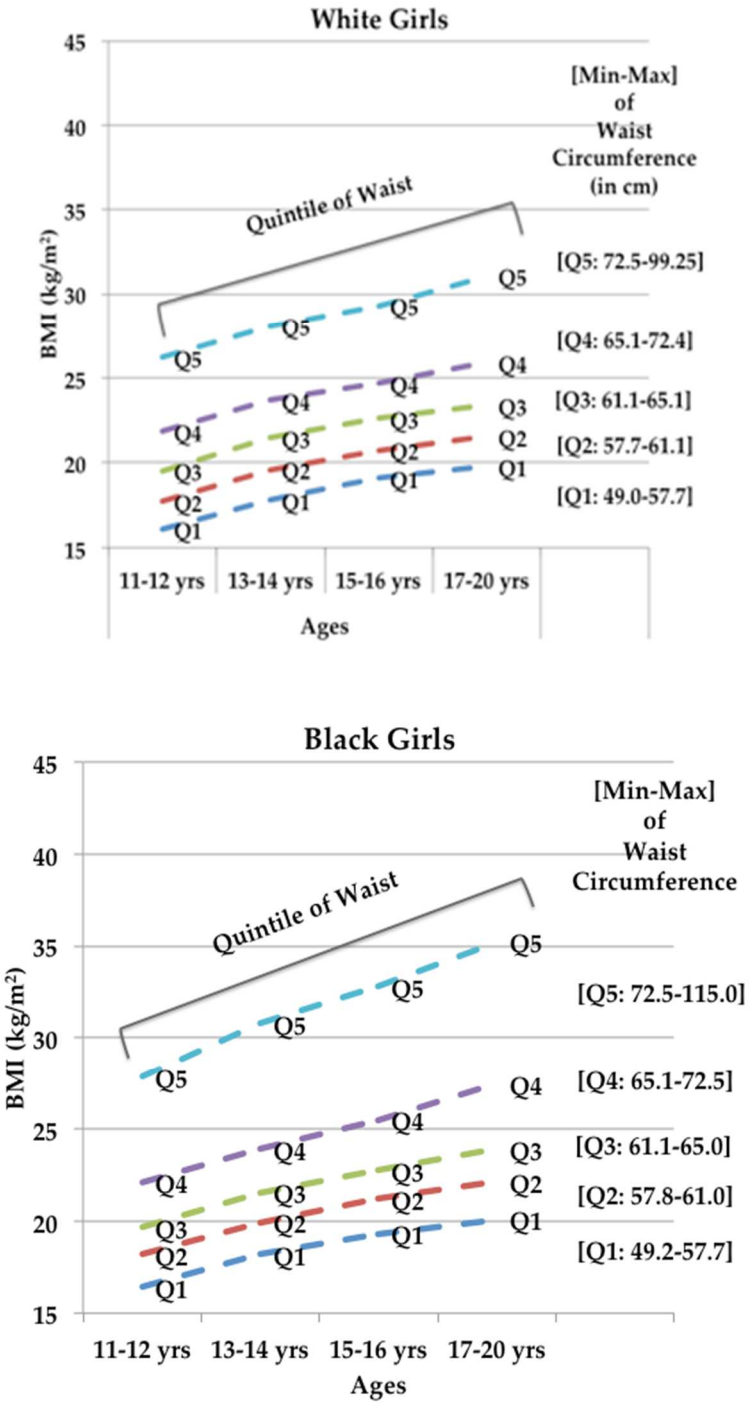


Figure 2.3. BMI tracks throughout childhood according to quintiles of early WC (ages 9-11 yrs)



While early adolescent black girls had significantly lower average percent body fat (22.1% vs. 26.3%) than whites at 9-10 years of age (Figure 2.4), they gained fat more rapidly (45.1% vs. 25.9% increases, in blacks and whites, respectively). At 17-20 years of age, average percent body fat in whites was 30.1% and in black girls was 31.8%.

Figure 2.4. Average increases in % Body Fat between early and late adolescence in black and white girls

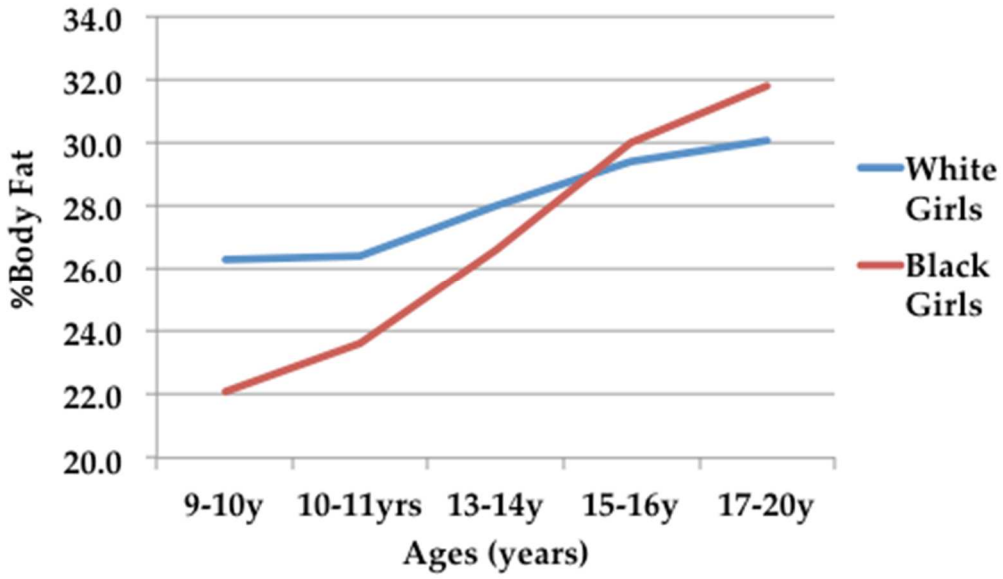


Table 2.4. shows the stability within quintiles body fat exposures. Among girls in Q1 (quintile 1) of BMI at baseline, ages 9-10, 60.5% remained in that quintile at the end of adolescence. Similarly, 70.3% of the girls who started in Q5

of BMI at baseline remained in that quintile at the end of follow-up. In these results, there was less stability in the classification of percent body fat than there was for BMI and WC.

Table 2.4. Percent of girls at baseline who remain in the same quintile of a given body fat measure as at 17-20 years

BMI	ages 17-20 ➔	Q1	Q2	Q3	Q4	Q5
ages 9-10	Q1	60.5%	28.1%	7.6%	3.0%	0.8%
↓	Q2	25.5%	34.2%	26.9%	11.8%	1.9%
	Q3	10.3%	23.2%	37.1%	24.7%	4.9%
	Q4	3.4%	12.9%	23.5%	38.4%	22.1%
	Q5	0.4%	1.5%	4.9%	22.1%	70.3%
WC	**ages 17-20 ➔**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
ages 9-11	Q1	54.6%	30.0%	10.7%	4.9%	0.4%
↓	Q2	25.6%	33.5%	24.7%	14.5%	1.9%
	Q3	14.5%	23.6%	34.2%	22.4%	4.9%
	Q4	4.2%	10.7%	27.4%	35.4%	22.4%
	Q5	1.2%	2.3%	3.0%	22.8%	70.3%
%BF	**ages 17-20 ➔**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
ages 9-10	Q1	48.1%	22.8%	16.4%	11.4%	1.5%
↓	Q2	31.3%	26.6%	19.9%	13.3%	8.4%
	Q3	11.1%	32.7%	25.6%	20.5%	10.7%
	Q4	8.0%	14.1%	26.0%	28.9%	23.3%
	Q5	1.5%	3.8%	12.2%	25.9%	56.1%

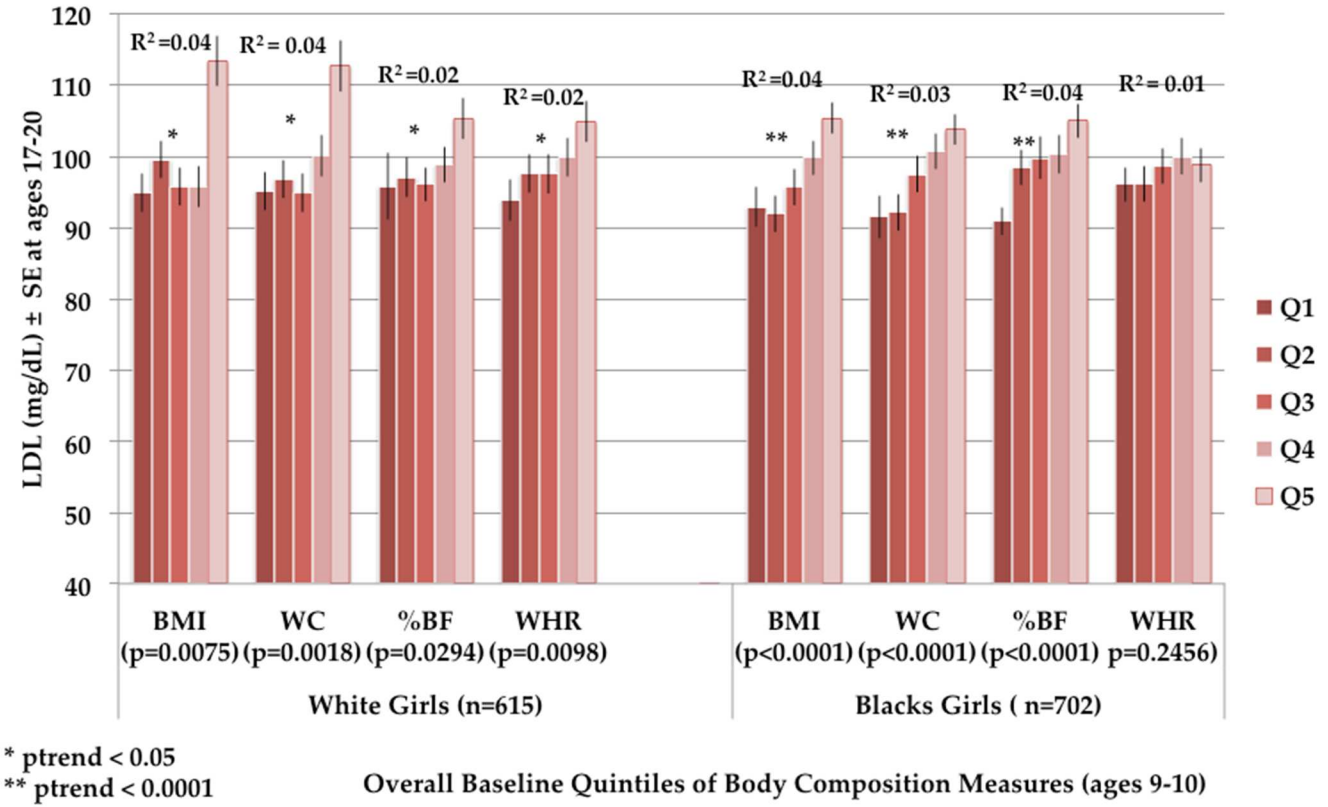
Comparing prediction of late adolescent lipid levels according to early body fatness measures (BMI, WC, %BF, WHR).

Figure 2.5 shows the relationship between baseline quintiles of body fat measures – BMI, WC, %BF, and WHR – from ages 9-10, with the outcome of LDL at ages 17-20. BMI and WC (9-10 years) predict increases in LDL at ages 17-20 in white girls. Generally, there is a trend that shows the most prominent increases in LDL between Q1 and Q5 of early body fat measures, with a p-trend across quintiles of BMI, WC, %BF, and WHR that is <0.05 in white girls, however this trend was not so linear for BMI and WC, where there is a pronounced increase in Q5. With the LDL outcome, in white girls, the most prominent differences were of approximately 10 mg/dL between Q5 and the lower quintiles 1-4: there appears to be a threshold effect of later LDL predicted when using early adolescent BMI or WC. The trend across quintiles is clearer in black girls with a p-trend of <0.0001 with BMI, WC, and %BF. BMI, WC, and %BF are comparable predictors of late adolescent LDL in black girls. The R^2 of 0.04 for white girls offers a modest but relatively stronger association between BMI and WC and later LDL. Among black girls, the trend across quintiles was more linear, and the strength of association between BMI and %BF was R^2=0.04. Early measures of

WHR in black girls was not strongly associated with later LDL, nor did it reflect any specific trend related to categories of waist to hip ratio ($p=0.25$). By contrast, the relationship between early WHR and LDL was fairly linear for white girls ($p=0.0098$).

Statistically significant increases in LDL, shown in Figure 2.5, were observed across quintiles of waist size in both whites ($p<0.0018$) and blacks ($p<0.0001$). Predicted LDL for white girls in Q5 with the highest BMI or WC at 9-10 years was the most different from LDL of black girls, compared to similar pairings with early %BF or WHR. Among whites, a higher WC (Q5) led to mean LDL levels of 112.0 mg/dL in later adolescence, which was 16.4 mg/dL higher than those of girls in Q1 (while the difference for blacks was only 12.2 mg/dL with a final LDL level of 103.6 mg/dL).

Figure 2.5. Baseline Quintiles of Body Fat Measures (BMI, WC, %BF, WHR) from ages 9-10 and LDL at ages 17-20 in White (*left*) and Black Girls (*right*)



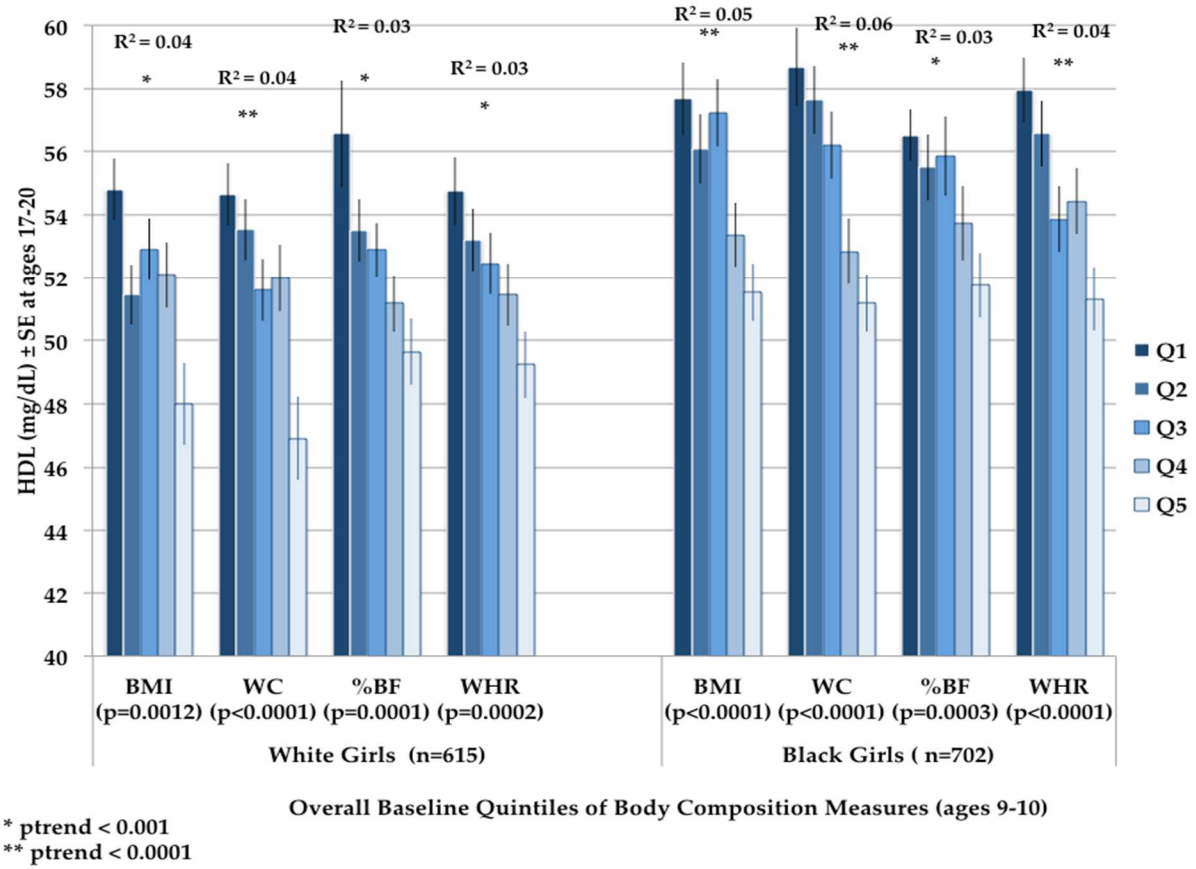
**Adjusting for baseline height (9-10y); menarche age; SES; average physical activity (9-17y)*

**For the ranges of values for each quintile of adiposity measure and Ns by race, please see Appendix A.2.3.*

Figure 2.6 shows the relationship between baseline quintiles of body fat measures – BMI, WC, %BF, and WHR - from ages 9-10, with the outcome of HDL at ages 17-20. Generally, HDL tends to decrease between Q1 and Q5 of body fat measures, with a p-trend across quintiles of BMI, WC, %BF, and WHR that is <0.001 in white girls. Increasing quintiles of WC, %BF, WHR are linearly related to later HDL in white girls. For BMI, the relationship was not linear for either white or girls; rather, being in the lowest versus highest quintile appears to be predictive of later HDL. In white girls, early adolescent WC was a good predictor of later HDL differences according to increasing levels of WC ($p<0.0001$), and was also related to HDL, $R^2=0.04$. The trend across quintiles is clearer in black girls with a p-trend of <0.0001 with BMI, WC, and WHR. In white girls, being in Q5 of early adolescent BMI and WC predicted a drop in HDL. Additionally, mean HDL in those Q5 white girls already spanned 45 mg/dL at baseline, an unhealthy level stated by the NHLBI for HDL for adolescents up to age 19 – Table 2.2). Black girls generally had higher HDL levels than white girls in each quintile of comparable body fat measure. As with later LDL, early adolescent BMI and WC are predictors of HDL in black girls, and slightly more strongly associated with later HDL than %BF or WHR with the $R^2=0.05$ and $R^2=0.06$ respectively (similar in white girls). Early measures of WHR in black girls

were a better measure of later HDL than LDL, reflecting a linear downward trend across increasing quintiles of WHR. As with later LDL, WHR was also linearly associated with later HDL among white girls. Racial differences in later HDL were prominent in inter-quintile differences between the highest early waist size group, Q5, and Q1, the lowest early waist size group. White and black girls, respectively, in Q5 of WC at 9-11 years of age had HDL levels that were 8.2 and 7.0 mg/dL lower in late adolescence than those of girls in Q1.

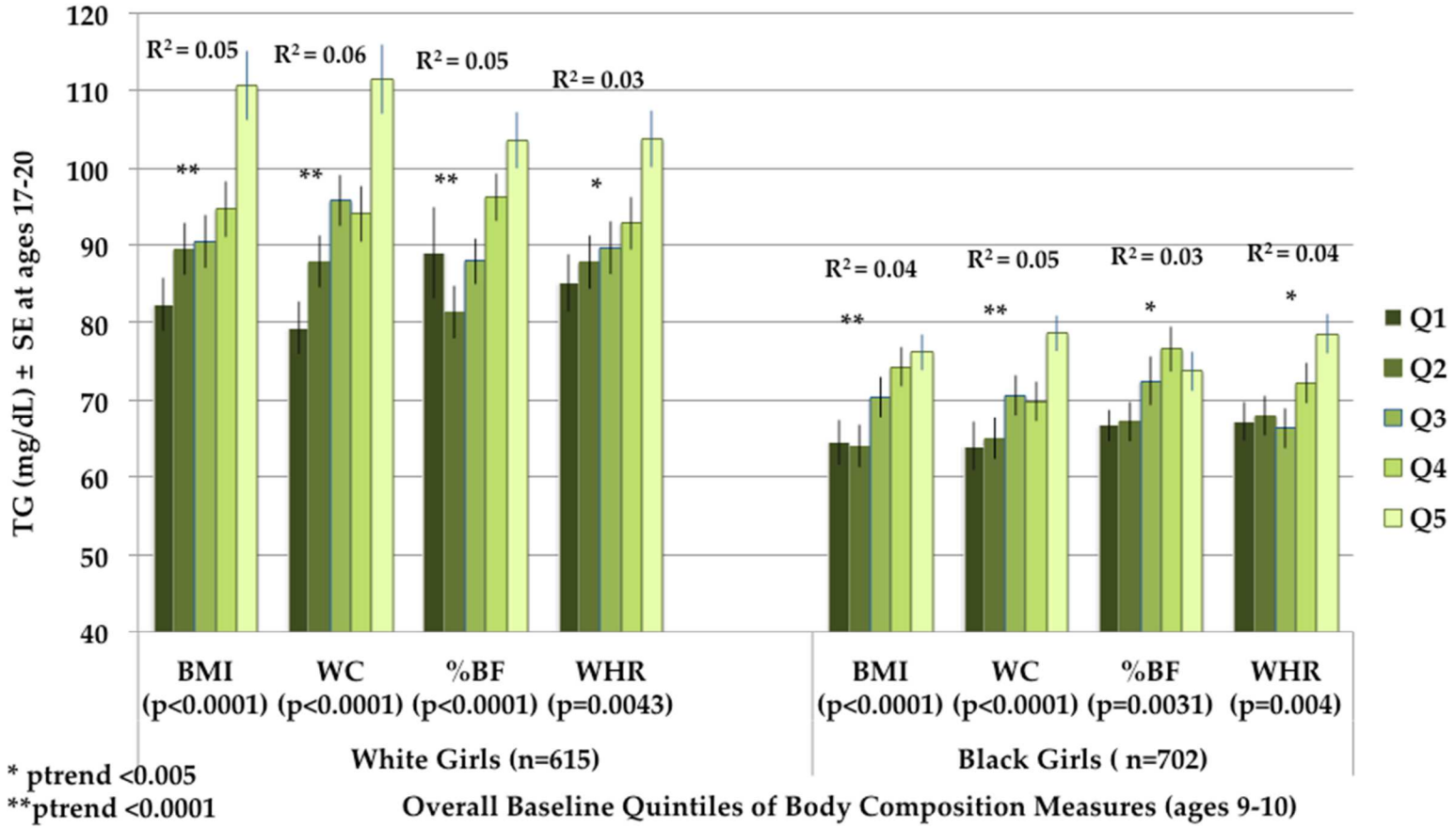
Figure 2.6. Baseline Quintiles of Body Fat Measures (BMI, WC, %BF, WHR) from ages 9-10 and HDL at ages 17-20 in White (*left*) and Black Girls (*right*)



**Adjusting for baseline height (9-10y); menarche age; SES; average physical activity (9-17y)*
**For the ranges of values for each quintile of adiposity measure and Ns by race, please see Appendix A.2.3.*

Figure 2.7 shows the relationship between baseline quintiles of body fat measures – BMI, WC, %BF, and WHR - from ages 9-10, with the outcome of TG at ages 17-20. The relationship between early adiposity, especially BMI, WC, and WHR) and TG appears to be fairly linear among white girls, but this trend is not particularly prominent among black girls, as the difference in TG between Q1 to Q5 is narrower for black girls compared to white girls. White girls' TG tended to exceed that of black girls. Generally, there is a trend that shows increasing TG across increasing quintiles of body fat measures, with a p-trend across quintiles of BMI, WC, and %BF that is <0.0001 in white girls and also across quintiles of BMI and WC in black girls. WC was particularly good at discriminating levels of later TG in white girls, R^2=0.06. WC was also more strongly associated with TG (R^2=0.05) than other measures of adiposity among black girls. Percent body fat was associated with later TG in white girls, R^2=0.05.

Figure 2.7. Baseline Quintiles of Body Fat Measures (BMI, WC, %BF, WHR) from ages 9-10 and TG at ages 17-20 in White (*left*) and Black Girls (*right*)



**Adjusting for baseline height (9-10y); menarche age; SES; average physical activity (9-17y)*

**For the ranges of values for each quintile of adiposity measure and Ns by race, please see Appendix A.2.3.*

Summary

BMI and WC appear to be more strongly associated with later adolescent lipids, but WHR is also often more linearly associated with later lipids in white girls. WC was a relatively good predictor of late-adolescent triglycerides and HDL levels in both whites and blacks while BMI was an equally good predictor of LDL. Figures 2.5-7 demonstrate that in late adolescent black and white girls, there were statistically significant trends of increasing LDL and TG and decreasing HDL levels across increasing quintiles of all body fat measures at 9-10 years of age. We observed a stronger association between early adiposity and later HDL in black versus white girls, and a stronger association between early adiposity and later TG in white versus black girls. Figures 2.6 and 2.7 show statistically significant decreases in HDL and increases in TG across quintiles of waist size in both whites ($p<0.0001$) and blacks ($p<0.0001$). By 17-20 years, white girls (vs. black girls) in the highest BMI quintile (Q5) had slightly higher mean LDL levels (113.4 vs. 105.1), lower HDL levels (47.9 vs. 51.6), and much higher triglyceride levels (111.2 vs. 75.6 mg/dL).

Racial differences associated with early adolescent body fat are more easily identified with HDL and TG than LDL. In black girls, the linear trends in later LDL across quintiles for BMI, WC, and %BF appeared to be more pronounced than in whites ($p<0.0001$). Trends of differences across quintiles of BMI, WC, and %BF were in fact stronger among black girls, for all lipid outcomes ($p<0.0001$).

2.4 Discussion

Early adolescent WC in 9-11 year old black and white girls predicted statistically significant increases across quintiles of waist size in almost all lipid outcomes in young adult white ($p<0.05$) and black women ($ptrend<0.0001$) ages 17-20 years, except for HDL, which decreased. The R^2 of the association between early adolescent anthropometric measures of body fat and LDL, HDL, and TG was generally slightly better for BMI and WC compared to %BF and WHR. The R^2 are notably low: this makes sense because of the subgroups of our sample in which we perform these analyses, where it is reasonable that the detectable levels could be lower compared to that which might be observable in the large population. It is also true that certain measures may not lend themselves to being predicted statistically with a high degree of R^2, adding to the importance of

sharing this work in the context of the larger literature on early adiposity prediction of later lipid outcomes among adolescents. Except for LDL in black girls, quintiles of early adolescent WHR were more linearly associated with LDL, HDL, and TG compared to other anthropometric measures.

Early adolescent WC and WHR in 9-11 year old white and black girls were more linearly related with later HDL, and TG (but not LDL). For prediction of later lipid levels, it is possible that waist size tells a part of the story about the significance of fat depots associated with body shape, and lipid levels. With LDL, it is uncertain why WHR is not a good predictor of adiposity-related trends in black girls. It is possible that there may be body shape differences with deposition of fat during puberty in black girls, which could complicate the relationship between early adiposity and later lipid levels. There appears to be a unique relationship between the adiposity captured by BMI and WC and later LDL in white girls, by which being in the highest quintile matters more for predicting higher levels of LDL than having lesser levels of adiposity. WC was, however, a stronger predictor of subsequent low-density lipoprotein (LDL) levels than other measures of body fat (LDL of Q5-Q1 of WC: 29.5 mg/dL in whites; Q5-Q1: 17.9 mg/dL in blacks).

The R^2 of the association between early adolescent anthropometric measures of body fat and LDL, HDL, and TG was generally slightly better for BMI and WC compared to %BF and WHR, and could suggest these are fine measures to predict HDL and TG, even if the linear trend is not strong for white girls with LDL.

In these prospective analyses, WC at 9-11 years of age was a statistically significant determinant of late adolescent LDL, HDL, and TG levels in black adolescent girls and a determinant of LDL and TG levels in white girls. In general, both WC and BMI were overall better predictors of later lipid levels than %BF. WHR was a stronger predictor of lipid levels in whites than in blacks. These results suggest that WC is a simple anthropometric measure of body fat in pre-adolescent girls that may be useful in identifying girls who are at risk for abnormal lipid levels by the time of later adolescence. However, it was not possible to conclude that WC was a superior measure in the case of all lipid outcomes in both blacks and whites. Black girls had significantly lower pre-adolescent %BF (23.6% vs. 26.4%) than whites, but gained fat more rapidly (34.7% vs. 14.0% increases), exceeding whites in %BF by late adolescence.

Regardless of race, BMI predicted higher levels of LDL and HDL (high-density lipoprotein). The CDC BMI for age charts for girls ages 9-10 indicate overweight at 85-95th percentile ranging from 20-22 kg/m^2 – 21-24 kg/m^2, and obesity at greater than 95th percentile, from 22-24 kg/m^2 and greater. In NGHS, girls who are in the highest two quintiles (top 20%) of BMI or WC by ages 9-10 are classified as overweight, and the top 10% are classified as obese (Table 2.1). White and black girls who fit this description may benefit from screening of other concurrent lifestyle behaviors, such as diet or lifestyle to monitor any overweight-related impacts on later lipid levels to keep them within healthy range. Black girls reach menarche earlier than white girls, and since we found menarche age to be a confounder of the relationship between early adiposity and later lipids, it may be useful for clinicians to consider menarche age in conjunction with their assessment of adiposity and associated risks with having greater body fatness during adolescence.

There are racial differences in lipids, consistent with prior work both in NGHS and other studies, such as the Bogalusa Heart Study(163), and largely in association with greater overweight among black girls. In our study, early anthropometric measures of BMI and WC are similarly able to predict later LDL,

HDL, and TG in both white and black girls. Risk of higher levels of lipids in young adulthood is evident and simple anthropometric measures as BMI and WC could serve as useful, non-invasive clinical tools to identify at-risk adolescents before many of them become obese; this could be in addition to standard monitoring of blood lipid panels for prevention of more serious cardiometabolic risks.

While we could have looked at BMI continuously by weight-for-age z-score, or categorically as overweight/obese/normal this would have limited our ability to do a direct comparison since similar scales are not widely used and accepted for WC, WHR, %BF. Instead, we looked at early anthropometric measures by quintile categories, which allowed us to get a sense for the trends in later lipids with respect to early anthropometrics. For a lipid outcome such as TG that tended to be linear across quintiles of BMI or WC, it could make sense to look at BMI or WC as continuous exposures. For LDL, where there appears to be a threshold of BMI or WC beyond which additional risk of higher levels of later lipids arises, sensitivity analyses around cutoffs for BMI or WC that are useful for predicting later LDL may provide helpful insights.

Extensions of this work, even in NGHS, could classify older adolescent girls' lipids in terms of presence or absence of dyslipidemia based on early adiposity as we did, or according to overweight or obese status. In a cohort with comparable participants of normal and obese body composition, and available later adolescent lipid measures, evaluating dyslipidemia as a categorical outcome may expand upon our findings based on early adolescent adiposity, and connect intermediate elevations in lipid profiles to dyslipidemia risk.

A number of studies have also considered the question of identifying early risk factors useful to predict later lipids or mechanisms for how a poor lipid profile may manifest as later cardiovascular disease. These included autopsy studies within the Pathological Determinants of Atherosclerosis in Youth (PDAY) and the Bogalusa Heart Study, and distributions of lipids in child and adolescent populations in NHANES. Guidelines for classifying adiposity-related risk factors have been established in adults and with some agreement, although, to a lesser extent, in children and adolescents. Cutoffs for female adults are the following: waist size ≥88 cm(164), and overweight at end of follow-up was defined as BMI > 25 kg/m^2 and BMI > 30 kg/m^2 or obesity (recommended by the National Heart, Lung, and Blood Institute and North American Association for

the Study of Obesity expert committee(138) and adopted by the World Health Organization)(15).

There is still much disagreement concerning the utility of categorical classifications of adiposity of BMI or WC, for example, in children and adolescents as meaningful predictors of health outcomes. Normal BMI, for instance, depends on a child's age. Instead, percentiles for age are often used; 85th percentile defines overweight, and obesity is defined as of the 95th percentile(165–167). Similar guidelines are not widely used for WC, and are not agreed upon for use in children and adolescents. Using the Center for Disease Control growth charts, and looking at our Figure 2.3 of BMI tracking with WC, NGHS girls in our study sample who are in higher baseline quintiles of Q4 for WC and have average waist sizes between 65.1-72.5 cm from ages 11-21, and are considered overweight (with BMI of 22-26 kg/m^2) using the BMI metric; those in Q5 for WC (72.5-115 cm) are obese already (with BMI of 27-31 kg/m^2) by age 13. The relationship between BMI and WC suggests that perhaps early WC may capture information about overweight and obesity trajectories during adolescence, and that these two measures could be useful together to predict

health outcomes, in addition to later lipid levels as we demonstrate in our results.

While we are curious about WC and WHR for what these measures could tell us about the impact of distribution of body fat and body shape on lipid levels relevant to health outcomes, some have also suggested another waist measure, WHtR, as a comparable way to standardize waist circumference as surrogate measures of abdominal adiposity(168). In adults, using a large, nationally representative sample from NHANES showed that WHtR, BMI, and WC were similar indicators of body fatness and were more closely correlated to each other than to %BF but could still distinguish categories of %BF by sex and age(140). Another study in children aged 5-16 years suggests that WHtR is more closely linked to childhood morbidity than BMI(144) and that it ought to be used as an alternative measure to BMI in children as well as in adults. Yet, it is still not definitive whether WHtR is superior to WC, or if these surrogates of abdominal adiposity are superior to BMI. Because WC changes occur rapidly and is at times irregularly with growth, particularly around puberty, waist-to-height may prove challenging and may not be a very stable anthropometric early measure of body composition. A small study of 75 children aged 3-7 years(169) did not find WHtR

to be superior to WC or BMI to estimate body fatness, nor did it correlate with CMR factors including LDL, TG, and HDL. From a measurement standpoint, adding two measures, waist circumference, and height also could introduce more instances of error into a predictive body composition measure, which would not be preferred. Alternatively, future analyses could look at height change in a regression model and perhaps smooth out growth patterns. Further studies could also make strides to justify standardization for multiple predictive tools that can capture body composition and adiposity.

Despite a lack of agreement in classifications of what constitutes elevated risk for cardiometabolic risk factors, as a whole, early adiposity has promise as a potential tool to use to examine possible risk of abnormal lipid levels in young black girls. The 2008 clinical statement "Lipid Screening and Cardiovascular Health in Childhood(170)" reemphasized the point that overweight children are a special risk category that needs cholesterol screening regardless of family history or other risk factors. This statement included then-new data on the importance of following the Dietary Guidelines for Americans, and of physical activity and fitness, along with data on pharmacologic treatments of dyslipidemia; as such, it replaced the 1998 policy statement, "Cholesterol in

Childhood" from the American Academy of Pediatrics. The statement also encouraged pediatricians to take a lifespan approach to prevention of cardiovascular disease in their patients, including screenings for potential risk factors, such as high LDL, low HDL, elevated blood pressure, concurrent type 1 or 2 diabetes mellitus, smoking, and obesity. The data we provide here supports this lifespan approach, and the conclusion that improving lipid and lipoprotein concentrations as early as early childhood and adolescence could contribute to lowering lifelong risk of cardiovascular disease.

While we directed our attention to comparing early adolescent measures of adiposity to predict later adolescent lipid levels, prior work in NGHS(171) has examined cases of unhealthy lipid levels, finding that there were 457 cases of elevated LDL, 584 cases of low HDL, and 254 cases of hypertriglyceridemia. A union of our work here discussing tools for using early adiposity to predict later lipids with guidelines for these lipid outcomes could be helpful way to employ preventive measures among overweight children and adolescents in clinical practice. The International Diabetes Federation and National Cholesterol Education Program (NCEP) have suggested cutoffs for these lipid and lipoprotein concentrations. Triglycerides or low-density lipoprotein ≥110 mg/dL,

high-density lipoprotein ≤50 mg/dL are considered high risk by the International Diabetes Federation, the National High Blood Pressure (HBP) Education Program Working Group on HBP in children and adolescents, and the NCEP guidelines for children and adolescents(39,172). While the later lipid levels of white girls in this NGHS population in Q2 and greater at baseline (Table 2.2) or in the highest quintile of BMI or WC had TG levels at ages 17-20 (Figure 2.6) that exceeded the desired NCEP level of <100 mg/dL in adolescents up to 19 years of age. White girls in the highest quintile of BMI or WC had low levels at baseline (Table 2.2), and some below 45 mg/dL putting them in an unhealthy range(173). Further, HDL tended to decrease in white girls with increasing body fatness.

Possible Mechanisms

Although we did not have biological measures of inflammation, such as c-reactive protein, conceivably, one landmark of excess stored body fat is a pro-inflammatory environment(134,174). Chronic inflammation, particularly, beginning early in childhood and progressing throughout adolescence may predispose adolescents to dyslipidemia. An inflammation hypothesis could reflect the actual inner state of metabolically active visceral fat depots that may be associated with elevated circulating lipids.

Roles of height and menarche on adiposity

Our final models of later lipids with respect to early anthropometrics include confounders that point to the possibility of a few non-modifiable, and modifiable factors that could impact later lipids. Baseline height, and SES are non-modifiable factors. Using height in modeling of risk in children and adolescents is complicated by the fact that it could be a surrogate of normal development, and/or pubertal development: girls who are more advanced in puberty will be taller as a result of the pubertal growth spurt. Height was a strong predictor, and also a confounder of the relationship between adiposity and later lipids in several instances in our analysis. While it is possible that modeling height and menarche age could explain more of the variability in trends observed related to maturation, the absence of consideration of maturation or normal growth would have made or findings perhaps less valuable. A way around this for future additional analyses could be to look at height velocity as a surrogate for growth in lieu of height. Menarche age is in the short term, non-modifiable, with the coding for puberty embedded in genes and possibly alterable by environment. Average physical activity from ages 9-17 was a confounder, and is a modifiable intermediate.

The impact of maturation on the influence of early body fat on lipid concentrations in late adolescence adds another interesting dimension. Our finding of WHR predicting linear trends in LDL, HDL, and TG with the exception of LDL in black girls suggests there may be other factors, perhaps racial differences, due to changes in body shape during the course of pubertal maturation, which could impact waist and hip classification in black girls. There are important differences in lipid levels, influenced by puberty and race(170). Berenson et al. (175) hypothesize that changes in serum lipoproteins during adolescence and sexual maturation could reflect the influence of sex hormones on lipoprotein metabolism. In a 3-year longitudinal study in both boys and girls, Kwiterovich et al(176). saw that in pubertal children, sexual maturation (determined by Tanner stage) was the factor associated with the greatest difference in LDL. Girls who were at Tanner stage 4 had average LDL of 0.274 mmol/L lower than those in Tanner stage 1. Consider that the average age of menarche in NGHS is between 12-12.7 years. This falls at just about the age of 13 years, which Sun et al. determined in the Fels Longitudinal Study to be the age beyond which a waist size of about 70 cm in adolescent girls could predict metabolic syndrome(164). NHANES data also suggests that total cholesterol

concentration peaks at 9-11 years of age at 171 mg/dL(177), decreases during puberty, and increases afterwards, suggesting that maturation is indeed important in clinical screening(178).

While we selected age at menarche as our landmark of pubertal tempo, it is important to note that there are other measures of puberty, such as Tanner stages, which we did not examine (other than to corroborate and establish each girl's age at menarche) that may provide additional insights into the role of puberty. Additionally, comparing our work here with future studies which use alternate measures of pubertal stage or age would help clarify the extent to which puberty may be important when measurements of early anthropometrics are used to look at prediction of later adolescent lipid levels. Since some girls, particularly black girls, had already commenced puberty at the start of the study, choosing to use an alternate measure of pubertal stage to menarche age in a follow-up study could perhaps integrate the contribution of those who began puberty earlier, and allow us to look at any unique metabolic trends related to early puberty. We saw it important to engage maturation in this study analytically because it does affect adiposity and the hormonal and developmental milieu around metabolism, and adjusted for menarche age as one

way to mark pubertal timing, Additional studies could not only compare similar models to ours using menarche age or pubertal stage to mark maturation, but also explore potential mechanisms relating maturation to other modifiable lifestyle factors important in adolescents, such as diet, physical activity, sedentary behavior, and psychosocial stress(37,179). Today, the trend for earlier onset of puberty(179) may be impacted by a variety of genetic and environmental influences. By virtue of this, it is possible to view decreasing menarche age or early puberty as intermediate risk factors for changes in lipid levels that may be potentially modifiable over time by addressing the factors that may be affecting pubertal timing, although much more research is required in this area. It is possible that adolescence is a sensitive time period that may set the stage for later metabolic health, underlining the need to better understand the biological and metabolic effects during maturation.

Strengths

We contribute findings from a large biracial, prospective cohort to this body of knowledge in the hopes of strengthening our understanding of possible causes of disparities health vulnerabilities in adolescent girls. We hope that this work will expand the useful criteria for early assessment of cardiometabolic risk

and highlight the integrated way that many biological, environmental factors interact to increase the overall cardiometabolic risk of a developing child. Suggesting a clinical use for BMI and WC as anthropometric, non-invasive predictors of later lipids is potentially valuable to clinicians seeing pediatric patients.

Limitations

The results of these analyses are limited to females and the conclusions reflect trends in black and white girls only. The Bogalusa Heart Study compared serum lipid differences in black and white girls and boys, and sought to account for differences in lipids by sexual maturation, obesity, smoking and other covariates(163). Combining their approach with ours in a suitable prospective cohort, could help to explain variability in lipid trends and also indicate which measures of early anthropometrics would be most useful for black and white adolescents. Differences in activities that young people do today due to cultural changes may alter the effect of potential confounding factors such as activity or television on body weight and adiposity. While menarche age provided some important insights about optimal time to look at body fat predictors in adolescent girls, there could be potential challenges with implementing

menarche age in future models of elevated lipid levels that precede dyslipidemia. Classification of girls by menarche status at the time when her waist size was measured may bring in error due to self-report of their age of menarche. For example: some girls may not understand the concept of menarche clearly, and may answer differently in different exam years. Corroborating their self-reported responses with that of a parent or guardian and a physical exam could, however, ensure consistency in reporting of menarche age.

Another limitation is that while this study is longitudinal over 10 years, follow-up is not long enough to monitor if those who appeared to be on a trajectory for increased risk actually go on to develop cardiovascular diseases that usually manifest later in adulthood. Future studies, which can repeat these findings using a longitudinal cohort, and even extend back with a birth cohort, could be important assets in providing evidence for pre-clinical screening of early indicators of dyslipidemia. Finally, the time of data collection in NGHS – late 1980s-90s - may limit the interpretation of these results for current adolescents. At the time of the original NGHS study cohort, the attention to and detection of the prevalence of obesity and overweight was not as common as it is today. Additionally, total cholesterol levels in U.S. adults and adolescents have

been falling since the late 1960s(177), and it is important to understand what the current, relevant determinants of lipid levels are today. With the current emphasis on lifestyle changes in the education and clinical setting that push back on the obesity epidemic, today we might expect that among those older adolescents with higher lipids, the causes could be more complex and involve mechanisms apart from obesity.

While our results suggest that early measures of anthropometric measures from ages 9-10 provide insight into later lipid levels in adolescent girls, we did not examine if anthropometric measures are as good as predictors as the current recommended measure of lipid panels of early adolescent lipids at ages 9-10, or if both together add value in understanding the determinants of lipid-related cardiometabolic risks. While BMI and WC appeared to be better than %BF and WHR, it is important to note potential limitations in measurements which could impact this. BMI and WC each require a single measure. WHR is a ratio of both waist and hip – two measures – and thus additional measurement error could potentially impact the stability of this measurement (although it should not affect a consistent comparison as we do across all lipid measures, and both races). %BF in this study was calculated from race-specific FFM equations, and not measured

directly through DXA; as a result, it is conceivable that this mode of classification of %BF could have impacted the stability of early adolescent quintiles of %BF – there is more movement in %BF across ages than with BMI or WC. Comparing the ability of BMI or WC and early lipid levels as predictors of later lipid levels could be an important and clinically relevant next step for this work. Since waist was measured in 9-11 year olds in our study sample, future analyses done should include BMI and %BF from age 11 as well as 9-10 so all ages compared in our sample would be from the same period.

We built on the cadre of existing knowledge about the associations between body fat and cardiometabolic risk to see if early, pre-adolescent measures can predict racial differences(121) in different risk factors, specifically in later lipids, which also may play a role in the development of other associated cardiometabolic risk factors like high blood pressure and insulin resistance. Prior work in NGHS(114) has elucidated the relationship between central adiposity changes in adolescence and prediction of cardiovascular risk. Our work may shed light on possible mechanisms for how body fat, and in particular, waist circumference, might reflect later lipid levels.

Our models that reflected the association between early adiposity and later lipid levels largely adjusted for non-modifiable factors, with the exception of physical activity. These findings also underline the known importance of physical activity in a healthy lifestyle, with potential far-reaching effects into adult metabolic health. We suggest BMI and WC, measured as early as 9-10 years, as useful predictors of later lipids.

This work advances the field by showing evidence that simple anthropometric measures of body fat (BMI, WHR, WC, %BF) in early adolescence, can predict higher levels of lipids in late adolescence, and before many of these young girls have become obese. The clinical value of this finding is that simple anthropometric measures such as BMI and WC could be useful first indicators of risk of later elevated lipids; they are easier to perform to assess metabolic risk in pediatric patients than a full lipid panel – currently recommended in lipid guidelines for 9-11 year olds. Our findings indicate simple anthropometric predictors of later lipid levels that could help as biomarkers of later adolescent lipids. Early identification of potential risk of dyslipidemia through simple, non-invasive methods holds great value for prevention of later risk of serious chronic disease in adults.

CHAPTER THREE: The role of early adolescent BMI and menarche age on the prediction of later lipid levels in later adolescence

3.0 Abstract

The role of adiposity at different time points in early adolescence on later lipid levels is not well understood. In particular, it is not known if pre-menarche measures of body fat will serve as important predictors of later lipid levels or if post-menarche measures will be stronger predictors. Our study sought to compare pre-menarche and post-menarche measures of body mass index (BMI) with respect to their prediction of later lipid levels. The National Heart Lung and Blood Institute's Growth and Health Study (NGHS) was used here to evaluate effects of early adolescent BMI in black and white girls on lipid levels in later adolescence. We used multiple linear regression analyses to attempt to understand the relationship between pre- and post-menarche measures of BMI and later adolescent lipids, and we controlled for confounding by demographic and behavioral risk factors. Pre- and post-menarche BMI was inversely associated with high-density lipoprotein (HDL) at ages 17-20. Post-menarche BMI was generally a better predictor of later lipids in white girls compared with pre-menarche BMI; pre-menarche BMI measures (HDL: R^2=0.03, p<0.0001) in

black girls, however, were either as good as or better (HDL: R^2=0.04, p<0.0001) than post-menarche. Post-menarche BMI predicted TG/HDL in white (R^2=0.05, p<0.0001) and black (R^2=0.05, p<0.0001) girls, and was similar pre-menarche. Higher levels of post-menarche BMI predicted linear trends in HDL (decreases) and low-density lipoprotein (LDL), triglycerides (TG), and triglyceride-to-HDL ratio (TG/HDL) (increases), particularly in white girls. In these analyses, BMI as an anthropometric measures of body composition taken less than 2 years post-menarche was a better predictor of later lipid levels than pre-menarche BMI however, pre-menarche BMI was slightly more strongly associated with later lipids in black girls. These results suggest that BMI, as a simple anthropometric measures of body composition, in adolescent girls may be useful as early as pre-menarche in black girls, but post-menarche measures may be more useful in identifying either white or black girls who are at risk for dyslipidemia by the time of later adolescence.

3.1 Background

The role of body composition at different time points in early adolescence on later lipid levels is not well understood. Some studies have looked at the associations between body composition and cardiometabolic risk factors,

including lipid levels, however, not with particular attention to the role of maturation, and with a longitudinal design for black and white girls(47,146,180). In particular, it is not known if pre-menarche measures of body fat, and in particular, BMI, will serve as important predictors of later lipid levels or if post-menarche measures will be stronger predictors.

To evaluate the value of body fat as a predictor of later adolescent lipid levels, we propose that it may be important to consider pubertal maturation(108,114–116). It is likely that the physical, hormonal, and behavioral changes during puberty may impact body composition and prediction of later lipid levels. Body composition, which includes total body fat, lean body mass, and bone mineral content, all increase during pubertal maturation and girls in NGHS accrue fat mass at a faster rate than fat-free mass between the ages of 9-10(152). In addition, black girls tend to go through puberty earlier than white girls, and their earlier early age at menarche(115) has been associated with concurrent metabolic abnormalities such as insulin resistance(117) and elevated blood pressure(118). Whether, and if so, how age of maturation affects later lipid levels are not well understood.

Prior studies concerned with maturation in adolescents have looked at a variety of contexts around the changing hormonal and body composition milieus around puberty. Pre-menarche body composition has been shown to predict weight status in black and white women. One study considered body fat deposition around the time of menarche and compared total body fat before and after menarche in European American and African American girls. They found that reproductive maturation was associated with accelerated fat deposition among African American girls that was doubled from their pre-menarche body fat(181). Pre-menarcheal weight status in the Newton Girls Study with a 30-year follow-up found that pre-menarcheal overweight weight status explained almost all of the variability in adult weight status(180). It is unclear whether the timing of adolescent body composition measurements is important for prediction of blood lipid levels in adulthood. The comparison of pre-and post-menarche measures of body fat could aid in understanding the evolution of racial differences in lipid levels that may affect dyslipidemia risk in young women. Further, comparison of pre- and post-menarcheal BMI could help to ascertain when BMI might best predict unhealthful lipid levels to prevent adverse health outcomes.

In addition to health risks associated with unhealthful levels of individual lipids, like LDL, HDL, and TG, the ratio of TG/HDL may provide additional insights into how lipid particle size may confer risk. One postulated mechanism for the action of dyslipidemia on risk of cardiovascular disease (CVD) relates to lipid particle size and density(182,183). A high TG/HDL suggests the presence of more small, dense LDL particles. In brief, small, dense LDL particles(184) and HDL particles (185) are associated with higher risk of CVD, while large, fluffy LDL is associated with lower risk of CVD. By this proposed mechanism based on lipid particle size(186), TG/HDL (187) is sometimes used as an indicator of atherogenic risk. The relationship between body composition in young adolescents and lipid particle size is unknown.

The objective of this study was to compare the race-specific (in black and white girls) effects of pre- vs. post-menarcheal BMI in young girls on lipid levels in late adolescence (at 17-20 years of age). Secondly, we sought to describe any racial differences in this determination of whether pre-or-post-menarche BMI is a better predictor of lipid levels in later adolescence.

3.2 Methods

3.2.1 Study Population

Data from the National Heart Lung and Blood Institute's Growth and Health Study (NGHS) was used for this study. Study participants in NGHS were recruited from three separate geographic areas to minimize the likelihood of biased results due to regional differences and to allow for comparison across socioeconomic backgrounds. Subjects were recruited from census tracts that had approximately equal black and white residents and the least disparity in education and income(122). Children were enrolled from three clinical centers: the University of Cincinnati/ Cincinnati Children's Hospital Medical Center in Ohio, Westat, Inc./Group Health Association in Rockville, Maryland, and University of California at Berkeley, in Berkeley, CA and were followed prospectively for 10 years. Berkeley and Cincinnati girls were recruited from public and parochial schools, and those from Westat were recruited from a health maintenance organization. The criteria for the selection of subjects and broad exclusion criteria from the original cohort have been previously described in detail(116–118). Research protocols were reviewed and approved by the NHLBI's Institutional Review Board. Measurements of exposures, outcomes, and

co-variables were evaluated according to study protocol at annual exams by examiners who were certified, monitored, and trained to use the NGHS protocol.

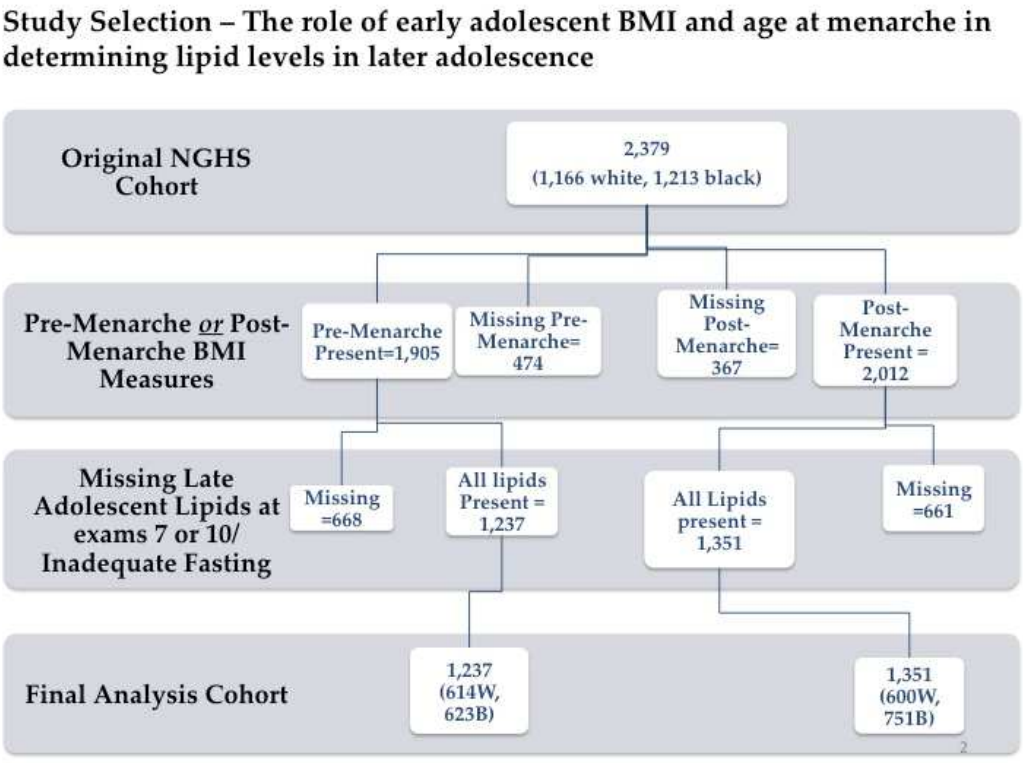
Inclusion and Exclusion Criteria

Eligibility Criteria: In brief, girls eligible for recruitment in NGHS had to meet the following criteria (a) within two weeks of age 9 or 10 at the time of the first clinic visit(120); (b) be self-defined as black or white and come from racially concordant Caucasian or African American households; and c) parents had to complete a household demographic form, give parental consent and the child also gave assent for participation in the study.

Study Selection Criteria: We studied 1,237 girls (n=614, white girls; n=623, black girls) with complete data for the exposure, pre-menarche BMI, within a rounded 1-2 years before each girl's menarche age, as well as the outcomes of LDL, HDL, TG, and TG/HDL at ages 17-20. We studied 1,351 girls (n=600, white girls; n=751, black girls) who had complete data on the same exposure and outcomes within a rounded 1-2 years after each girl's menarche age. We used mother's data in this analysis, and 2006 girls had information on one or more female relatives who filled out parent data forms. We compared the subjects who

were included with those who were excluded and there was no large or systematic difference between the two groups either pre-menarche or post-menarche.

Figure 3.0. Study Sample Selection Tree



3.2.2 Exposure Variables

Anthropometric Measures of Body Composition

Height was measured to the nearest 0.1 centimeter with socks using custom portable stadiometers, and weight to the nearest kilogram using an

electronic Health-O-Meter scale, in duplicate. A third measurement was taken if the two measures differed by more than 0.3 kg for weight or 0.5 cm for height. These were obtained for both mothers and their children. Body mass index (BMI) was the adiposity exposures that we used in our analyses. BMI was calculated from annual measurements as weight in kilograms divided by height in meters squared.

Sexual Maturation

Maturation was ascertained using age at menarche (average age of 12 in this cohort) (113) based on questions asked of the girls annually, and also assessed by trained nurses based on indexes of pubic hair distribution and areolar development. Trained nurses used modified Tanner staging principles from criteria developed by Garn and Falkner(162) that classified subjects into four maturational stages: 1) pre-pubertal (stage 1 of either areolar or pubic hair development, pre-menarcheal), 2) pubertal (pre-menarcheal and stage 2 or greater of areolar or pubic hair development), 3) <2 years post-menarche, or 4) >2 years post-menarche(124).

Determination of Individual Pre-Menarche and Post-Menarche Values of Measured Body Fat for Each Girl

We sought to identify a period sufficiently distant from the point of menarche to capture pre- and post-menarche measures of BMI that were not influenced by metabolic changes happening at the time of menarche. We established new pre-menarche and post-menarche baseline values of BMI, WC, WHR, and percent body fat as our exposures of interest. To accomplish this, we first ascertained a best estimate of every subject's age at menarche using a combination of data from both the girls' report of pubertal maturation and onset of menses as well as the study nurse report and assessment of Tanner stage. Specifically, we examined consistency in the year-to-year report from the girls regarding onset of menses as well as consistency between the girl and the nurse-based report of Tanner stage). Rules were used for handling inconsistencies in determining the final assigned age at menarche.

Prior methods(124) informed our approach: in this study, the authors classified maturation in girls as <2 years post-menarcheal or >2 years post-menarcheal. Given that the authors found that pubertal maturation post-menarche was approximately 2 years, we also tested pre-menarche of 2 years

before menarche age. To start, we conservatively tested prediction of lipids based on BMI, WC, WHR, and %BF from very close - 0.5 years - to a wider interval - 3 years - around menarche age to encompass this +/-2 year range. The Newton Girls Study, a study of pre- and post-menarche overweight and adult BMI outcomes, defined the menarche time period as one year - including 0.5 years before to 0.5 years after menarche. They operationally defined pre-menarche as 0.5-1.5 years before menarche, and the post menarche period as approximately 2 years after menarche(180). After testing these intervals in NGHS, we determined that Pre-menarche BMI ranged from 21.6 months before to 18.0 months after age at menarche, and post-menarche BMI ranged from 14.4 months after to 19.2 months after age at menarche. Pre-menarche and post-menarche BMI are operationally defined here as a rounded + or - 1-2 years from each individual girl's age at menarche. Next, to actually determine the adiposity, and LDL, HDL, TG and TG/HDL lipid levels, age, and height at both pre-menarche and post-menarche exposure times, we captured the exam visit that fell within the range months from each girl's age at menarche where she had data for the variables. In most cases, only one exam met the criteria. In cases where there was more than one, an average was taken.

3.2.3 Outcome Variables

In our study, we evaluated fasting LDL, HDL, and TG. Lipids were analyzed at Johns Hopkins Lipid Laboratory at exams 1,3,5,7, and 10. Lipid outcomes in our analysis included an average of all available lipids when the girls were 17-20 years of age. The ratio of triglycerides to high-density lipoprotein (TG/HDL) was calculated from mean values at ages 17-20. In NGHS, LDL was calculated using the modified Friedewald equation which estimated LDL-C by dividing TG value by 6.5 to provide a better estimate of LDL-C in children(154). For LDL, TC, and TG, 494 girls who reported fasting less than 8 hours were excluded(155). In our analyses comparing pre- and post-menarche body fat measures, we logarithmically transformed TG to normalize the skewed distribution of the data.

3.2.4 Potential Confounding Variables

Demographic Variables

Age was the exact age calculated based on the child's date of birth. Race/ethnicity was self-declared and collected at study entry. Categories of socioeconomic status (SES) were created by combining data on income and education as follows: (a) low - household income < $10,000, regardless of

education level or household income from $10,000 - <$20,000 and education level of high school or less; (b) moderate - household income $10,000 - <$20,000, household income $20,000 - <$40,000, regardless of education, or household income $40,000 or more with only a high school education or less, and (c) high - more than a high school education and an income of $40,000 or more.

Dietary Factors

A wide range of dietary variables was measured and available for use. Diet was assessed in 8 of the 10 total yearly exam visits (at years 1,2,3,4,5,7,8, and 10) using a 3-day food diary including two weekdays and one weekend day. To complete the diaries, girls were given instructions by registered dieticians and provided with a set of measuring cups, spoons, and a ruler along with a binder of illustrated instructions on how to record portion sizes for their food intake using household measures. Three-day food records were used to record dietary intake, and after these were completed, nutritionists interviewed the girls to verify the entries.

Food records from 2,147 (86% of the black girls, and 95% of the white girls) out of 2,379 girls enrolled in NGHS at baseline were received. To analyze

the nutrient content reflected in these records, they were entered into the University of Minnesota's Nutrition Data System (NDS)(156). The NDS system estimates daily intake of nutrients based on these food records. Servings of USDA-defined food groups (157)were derived from the NDS output by linking ingredient codes with food codes from the USDA's "MyPyramid Equivalents Database". Together, this provided each subject's nutrient intake along with intakes in all USDA food groups and subgroups, including but not limited to total energy, carbohydrates, protein, fat, dairy, fruit and vegetable, whole grain, and fiber. Average intakes from ages 9 to 17 were used in our analysis.

Physical Activity and Television

Physical activity patterns were assessed during administered structured interviews in study years 1,3, and 5 and then self-administered for years 7-10 where activity was measured by self-report in a Habitual Activity Questionnaire (HAQ) (adapted from Ku et al.(158)) that described exercise patterns of the last year(159). Standardization and optimization of data collection on physical activity in NGHS was established during year 7 of NGHS at the University of Pittsburgh's Physical Activity Resource Unit. Activity from physical activity

classes, sports in the school year or summer, summer physical activity, and activity in the rest of the year were summed for an overall physical activity score.

The HAQ score in MET-times per week in each of these categories was computed by multiplying the MET (metabolic equivalent, the ratio of metabolic rate during a specific physical activity to a reference metabolic rate, where 1 MET = 3.5 ml 0_2 kg^{-1} min^{-1} in MET/min/day) scores for activities by weekly frequency, and a fraction that reflected if the activity was completed during "most", "half" or a "small part" of the designated time of the year from the activity diary(160,161). These weekly summary scores were modified from those used in adult studies to reflect energy expenditure commonly associated with those activities for a given age and gender over the whole past year.

Television (TV) or video hours in half hour increments were collected in two ways: 1) hours usually watched were collected using a reference directory of specific programs (study years 1,3,5) updated annually, and 2) by report of TV hours usually watched (study years 6-10) during the morning, afternoon, and nighttime hours of a typical week (161). In a methodological test in the first exam, a subset of participants was asked about hours of TV usually watched

using listing of programs, and this was compared with the their response to a weekly estimate of the number of hours of TV, movies, or videos that they watched that week. Data captured from programs watched was found to be more accurate, and the first method was used in earlier exams. Average physical activity METs and TV or video watching hours per week between ages 9-17 was used in our analysis.

Maternal Factors

Parents provided data at study years 1,3,5, and 7. Biological mother's BMI was collected, at study years 1,3,5 and 7. The first available of these was selected as the mother's BMI in our analyses of the relationship between early factors on later child lipids. Mother's age at first period was ascertained by questionnaire at study years 1 and 3. Although we tested maternal factors in our preliminary models, we ultimately do not present final adjusted models with mother's BMI due to limitations we discuss.

3.2.5 Statistical Analysis

Baseline Data Preparation in Tertiles

Continuous early adolescent anthropometric measures of BMI for the overall study population were divided into tertiles (T1, T2, T3) for each exposure period – pre-menarche, and post-menarche. In Chapter 2, we used quintiles to study the patterns of how early measures of body fatness could predict later adolescent lipids. We observed important, clear trends for girls who were in Q5, the highest classification of adiposity, associated with higher lipids in contrast to those who were in lowest quintiles of adiposity. At times, these trends were not as clear for the intermediate quintiles, and here we decided to use tertiles to stabilize the analysis further, by collapsing the groups and making the analysis groups larger. For the purposes of these analyses, using overall tertiles instead of race-specific tertiles was deliberate: it allowed us to compare the same group of girls who were in the each tertile across anthropometric measures of body composition and lipids and assured that the same cutoff values were compared for black and white girls. While members of Q5 have the greatest risk, retaining Q5 as the highest exposure category and dividing the group into three groups with cutoffs between Q1, Q2-4, and Q5 would not work because of the issue of insufficient power in the extreme exposure categories.

Comparison of pre vs. post-menarcheal BMI as predictors of later adolescent lipid levels

Our objective was to compare measures of BMI taken before menarche with those taken after menarche as predictors of late adolescent LDL, HDL, TG, and TG/HDL. We classified each measure of body fat during the two exposure periods separately into tertiles, and compared mean lipid levels at the end of follow up across tertiles using analysis of covariance modeling. We explored potential confounding by examining variables commonly associated with body composition and lipids as potential confounders, including: new ages and heights corresponding to the pre- and post-menarche body fat baseline; average over ages 9-17 of TV/Video hours/day, physical activity, total cups of dairy, total cups of fruits and vegetables, percent of energy from total fat, dietary fiber, and protein; girl's age at menarche; mother's BMI, mother's age at first period, and socioeconomic status. We developed the model by examining these potential confounders with BMI. Many of these factors were predictors of different lipid outcomes but many were not confounders and therefore were not retained in the final models. Potential confounders that changed the effect estimate by more than 10% were retained in the final models. In the final models for all pre- and post-menarche BMI for blacks and whites separately, we retained child's height

at ages 9-10 years. We were unable to control for hip circumference in the multivariable models for WC due to collinearity between the two variables.

Since we had a larger sample size for the post-menarche analyses than pre-menarche analyses, we repeated all statistical modeling restricting the data set to those girls who had data for both pre- and post-menarche BMI. BMI was chosen for this subset out of all the body fat measures because it is a simple anthropometric measure that is more likely to be used in clinical settings, and the fact that our findings in Chapter 2 indicated that early adolescent measures of BMI predicted of later TG and HDL. Restricting the entire analysis to all girls who had both pre- and post-menarche measures of body fat would have diminished our study population significantly, so this allowed us to select a body fat measurement of particular interest to see if there were differences of note in prediction patterns.

3.3 Results

Baseline Characteristics

White girls were more often in the high SES groups within each tertile of pre-menarche BMI than black girls. White girls had lower HDL and higher TG

than black girls and in both racial groups, HDL was inversely associated with BMI. In pre-menarche, white girls in the highest tertile of BMI already exceed a cutoff for mean TG/HDL of 2.0 (2.45 ± 2.6), and is possibly indicative of an insulin resistant lipid profile(188). The average age at the time of pre-menarche, was between 11.0 and 11.6 years. Using the CDC growth curves for BMI by age, overweight at 85th percentile is a BMI of approximately 20 -21 kg/m^2, a value exceeded in T3 of both white and black girls. In post-menarche, average age of the girls is approximately 14 years, and overweight at the 85th percentile begins at 24 kg/m^2. Both white and black girls in T3 post-menarche are actually not only classified as overweight, but obese at 95th percentile for age and weight. Figure 2.2 in the previous chapter shows a frequency distribution of menarche age in black and white girls, showing that menarche age is shifted to the left in black girls, who achieve menarche at a younger age on average than white girls. The ranges of pre- and post-menarche values of BMI for white and black girls are shown in Table 3.2. It is also evident from the distribution of BMI that many of these girls are already quite overweight, even prior to menarche.

Table 3.1. Baseline anthropometric values for blacks and whites, pre- and post-menarche

Pre-Menarche[1]	BMI Tertiles of White Girls			BMI Tertiles of Black Girls		
Subject Characteristics	Tertile 1 (n=214)	Tertile 2 (n=231)	Tertile 3 (n=169)	Tertile 1 (n=198)	Tertile 2 (n=182)	Tertile 3 (n=243)
	(mean ± s.d.)					
Age (yrs)	11.6 ± 1.1	11.4 ± 1.1	11.3 ± 1.0	11.0 ± 0.9	11.0 ± 0.94	11.1 ± 0.97
Height (cm)	147.0 ±7.7	148.3 ± 7.5	149.0 ± 7.8	146.3 ± 6.7	147.3 ± 7.4	149.5 ± 7.3
BMI (kg/m^2)	15.8 ± 0.9	18.4 ± 0.9	23.3 ± 3.1	15.8 ± 0.9	18.4 ± 0.80	24.7 ± 3.9
LDL	96.4 ± 24.4	97.6 ± 26.5	111.2 ± 34.6	100.0 ± 24.4	98.0 ± 26.5	110.1 ± 26.8
HDL	57.3 ± 10.6	53.4 ± 10.1	48.5 ± 11.5	60.0 ± 13.5	59.6 ± 12.6	52.7 ± 13.1
TG	76.1 ± 27.4	80.2 ± 27.9	107.5 ± 75.8	70.1 ± 32.6	67.7 ± 25.8	82.9 ± 34.8
TG/HDL	1.42 ± 0.68	1.59 ± 0.73	2.45 ± 2.6	1.3 ± 0.77	1.22 ± 0.62	1.71 ± 0.89
[1]1-2 years before Menarche						

Post-Menarche[2]	BMI Tertiles of White Girls			BMI Tertiles of Black Girls		
Subject Characteristics	Tertile 1 (n=220)	Tertile 2 (n=219)	Tertile 3 (n=161)	Tertile 1 (n=230)	Tertile 2 (n=232)	Tertile 3 (n=289)
	(mean ± s.d.)					
Age (yrs)	14.6 ± 1.3	14.2 ± 1.2	14.1 ± 1.1	13.6 ± 1.1	13.6 ± 1.1	13.6 ± 1.2
Height (cm)	163.6 ± 6.4	162.6 ± 6.2	162.1 ± 7.1	161.3 ± 6.7	161.2 ± 6.1	161.4 ± 6.0
BMI (kg/m^2)	18.6 ± 0.97	21.5 ± 0.9	26.7 ± 3.5	18.5 ± 1.2	21.4 ± 0.8	29.0 ± 4.8
LDL	96.1 ± 24.6	99.8 ± 26.3	108.0 ± 34.7	98.4 ± 24.9	102.8 ± 26.7	109.2 ± 26.9
HDL	56.9 ± 10.4	54.3 ± 10.6	47.7 ± 10.8	59.9 ± 13.2	59.7 ± 13.4	52.7 ± 13.4
TG	76.8 ± 26.8	79.3 ± 29.0	105.9 ± 74.4	69.7 ± 33.4	73.2 ± 29.1	81.6 ± 34.0
TG/HDL	1.5 ± 0.8	1.8 ± 1.3	2.3 ± 1.6	1.1 ± 0.5	1.2 ± 0.6	1.5 ± 0.92
[1]1-2 years after Menarche						

Table 3.2 – Range of BMI for Pre-Menarche & Post-Menarche Girls

PRE Menarche (N=1,237)			POST Menarche (N=1,351)		
	W Age [9.0-15.2y]	B Age [9.0-15.0y]		W Age [10.5-18.0y]	B Age [10.2-18.3y]
BMI (kg/m^2)			BMI (kg/m^2)		
T1 (n=214W 198B)	[13.2 < 17.1]	[12.5 < 17.1]	T1 (n=220W 230B)	[15.4 < 20.0]	[14.6 < 20.1]
T2 (n=231W 182B)	[17.1 < 19.9]	[17.1 < 19.9]	T2 (n=219W 232B)	[20.1 < 23.1]	[20.1 < 23.1]
T3 (n=169W 243B	[19.9 < 35.0]	[20.0 < 36.3]	T3 (n=161W 289B)	[23.1 < 40.3]	[23.1 < 43.5]

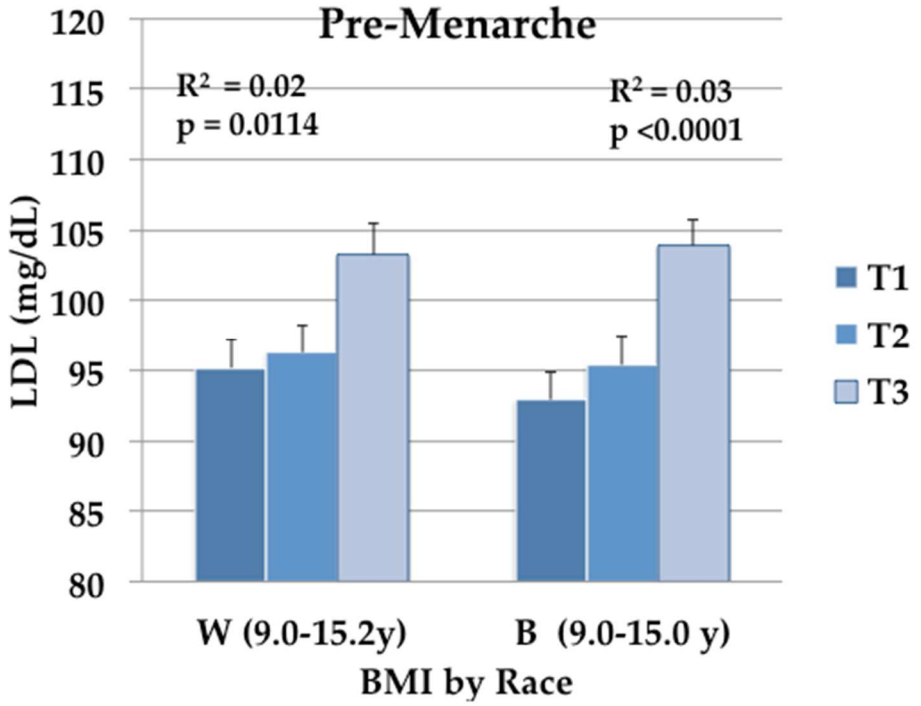
Comparison of pre- and post-menarche BMI values as anthropometric predictors of different late adolescent lipids

Final models in Figures 3.1-3.4 are adjusted for child's height at ages 9-10 years. Figures 3.1-3.4 show that BMI predicts later lipids both pre- and post-menarche. Figure 3.1 shows that black girls in the highest tertile of BMI have an LDL value that is 11 mg/dL higher than those in the lowest tertile of BMI. These results were the same, whether measured pre-menarche or post-menarche. In contrast, white girls with the highest BMI before menarche had LDL levels that were 8 mg/dL higher at 17-20 years of age while the highest BMI after menarche was associated with a 12 mg/dL increase in LDL.

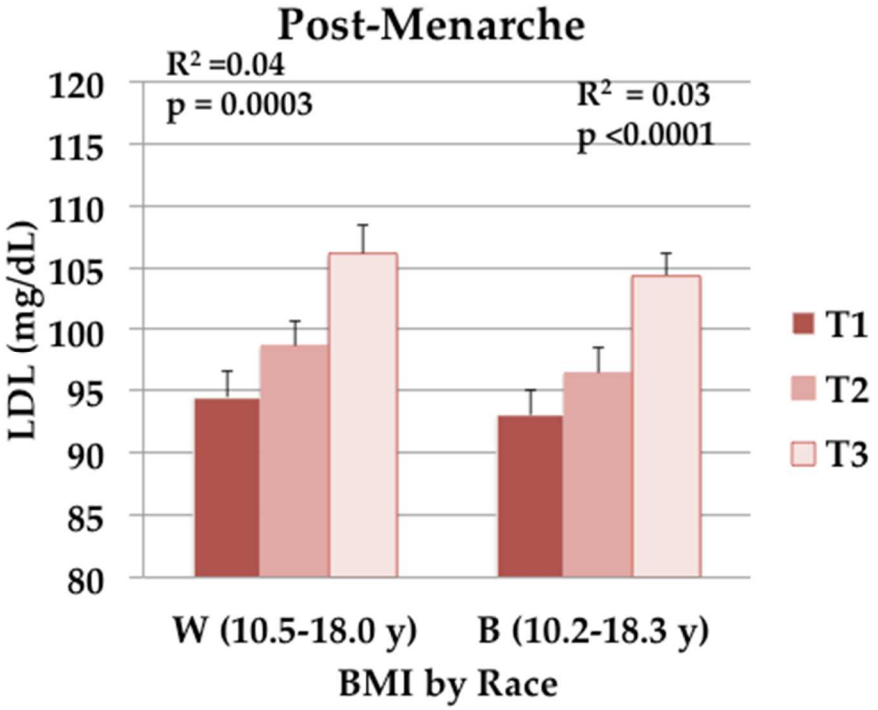
BMI is inversely associated with later HDL both pre- and post-menarche (Figure 3.2A-B), similarly in both white [Post-Menarche: R^2= 0.03, p<0.0001) and black (Post-Menarche: R^2=0.04, p<0.0001) girls. White girls have lower HDL levels than black girls, and girls who were in higher tertiles (e.g. T3) of BMI, had a lower HDL level at ages 17-20 compared to those who had less adiposity (T1). Post-menarche anthropometry is slightly more strongly associated with HDL, and is also generally better than pre-menarche at predicting linear trends in HDL in white girls: (R^2=0.02, p=0.0004, pre-menarche; R^2=0.03, p<0.0001 post-

menarche) In black girls, pre-menarche anthropometric measures of body fat were better than or as good as those post-menarche: (R^2=0.03, p<0.0001 pre-menarche; R^2=0.04, p<0.0001 post-menarche).

Figure 3.1. LDL at 17-20 years according to Tertiles of BMI, Pre-and Post-Menarche

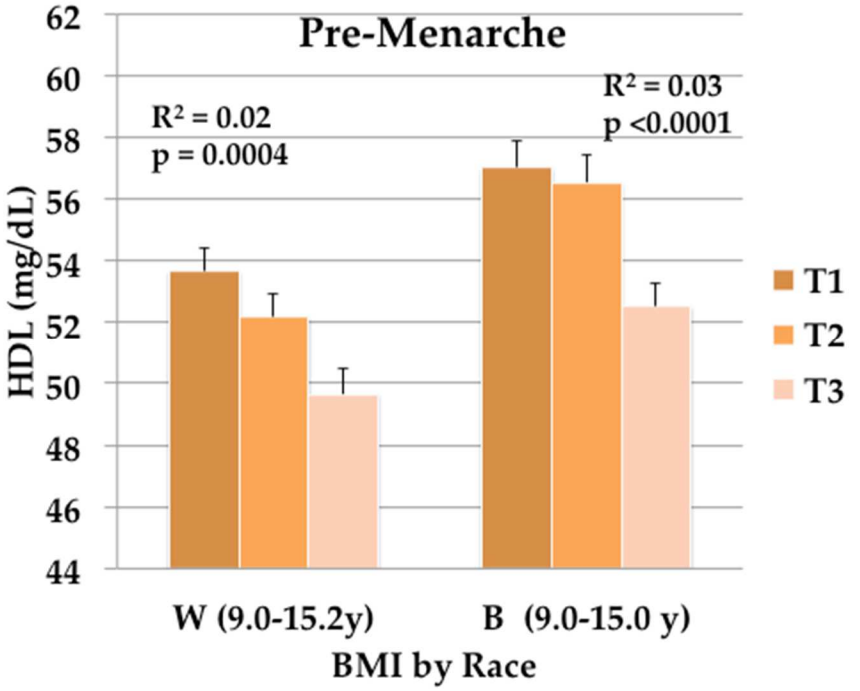


A

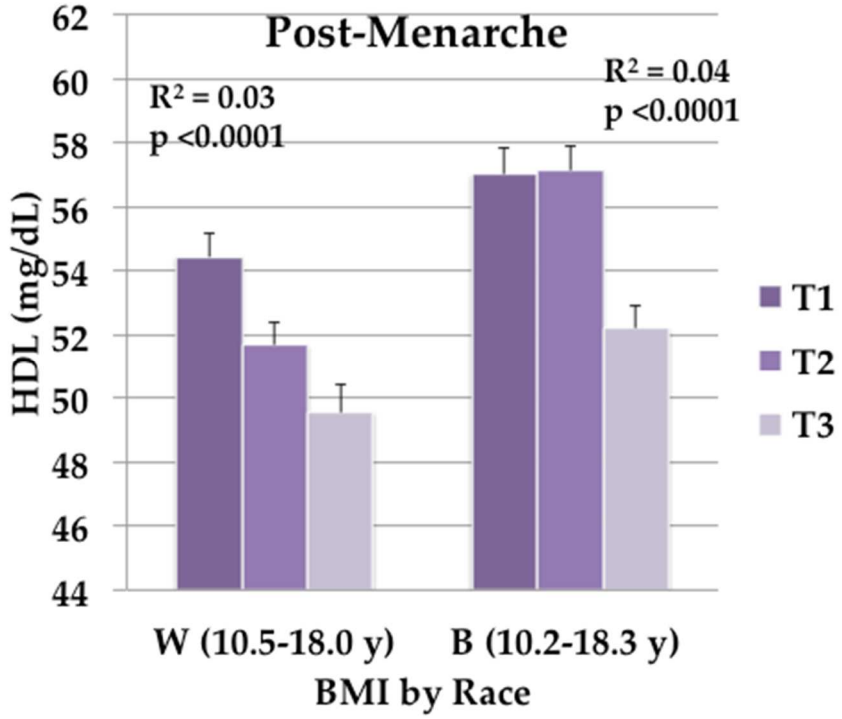


B

Figure 3.2. HDL at 17-20 years according to Tertiles of BMI, Pre- and Post-Menarche



A.



B.

Post-menarche measures of BMI (Figure 3.3AB) – in both blacks and whites more strongly predicted TG (ages 17-20) compared to pre-menarche measures of body fatness. As an example, post-menarche BMI, shown here, is a statistically significant predictor of TG in white girls ($p<0.0001$). However, while BMI predicted later HDL levels (shown in Figure 3.2AB) it is not quite as strong of a predictor of later TG (logarithmically transformed to normalize the results). Linear trends with BMI and HDL between ages 17-20 in black girls are inconsistent: they were more linear among white girls, either pre-or-post-menarche.

The linear relationship between either of the TG (Figure 3.3AB) and TG/HDL (Figure 3.4AB) outcomes and post-menarche BMI were similar. Post-menarche BMI was directly linearly related to TG and TG/HDL and was not linear for pre-menarche BMI in white girls; however in black girls, there is not a clear difference in when these early measures better predict later TG or TG/HDL (Figures 3.3-3.4). Increases in early BMI predicted increases in the TG/HDL ratio in whites in the highest tertile of BMI pre- and post-menarche (TG/HDL ratio=2.3). As tertiles of BMI increase in both races, the TG/HDL ratio also increases across tertiles. This trend and association of the relationship between

the TG/HDL and BMI was statistically significant in black girls (R^2=0.05, p<0.0001) both pre- and post-menarche. Increased BMI predicts an increase in TG/HDL both pre- and post-menarche.

Subset of girls with both pre- and post-menarche BMI data

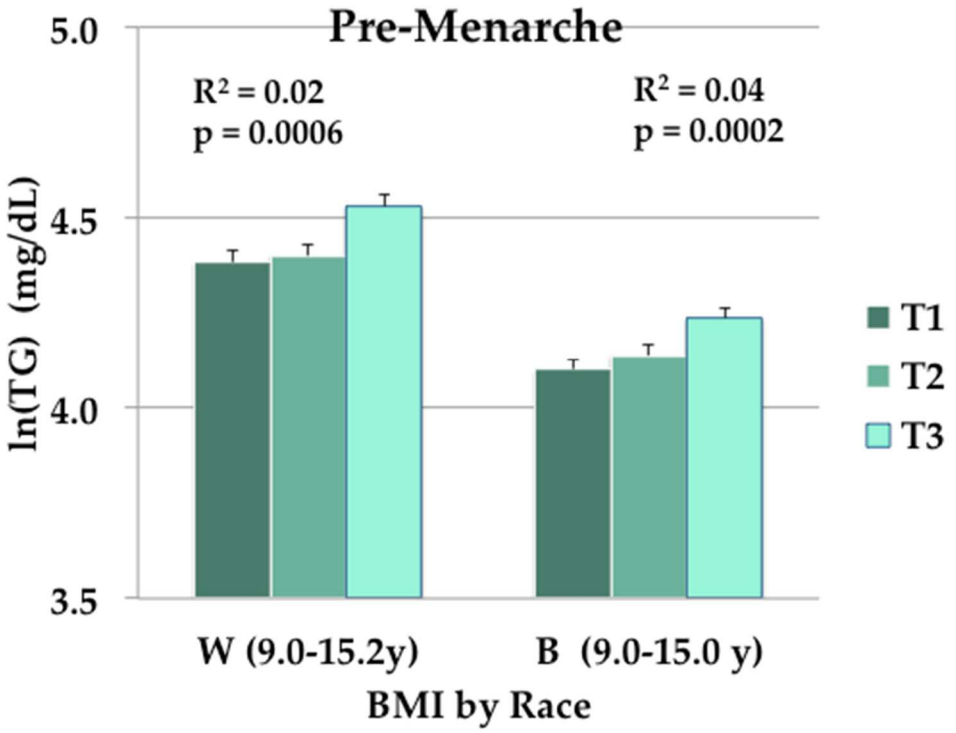
The analyses in Figure 3.2 depict the relationship between BMI and HDL with the maximum amount of subjects available for each pre- and post-menarche time point. A separate subset analysis of BMI and HDL (Table 3.3) containing the same girls who had both pre- and post menarche BMI data available as predictors of later adolescent HDL, showed no significant difference with the effect estimates (T3-T1) using the original reported results for Figure 3.2 or the subset sample with the same girls at both pre- and post-menarche time points (two-tailed t-test comparison of [Pre-Menarche: White girls: p=0.9779; Black girls: p=0.9241]; [Post-Menarche: White girls: p=0.9997; Black girls: p=0.9538]).

Table 3.3. Comparison of Mean Differences in Later Lipid Levels Across Tertiles of Early-Adolescent BMI in Same White and Black Girls Pre- and Post-menarche

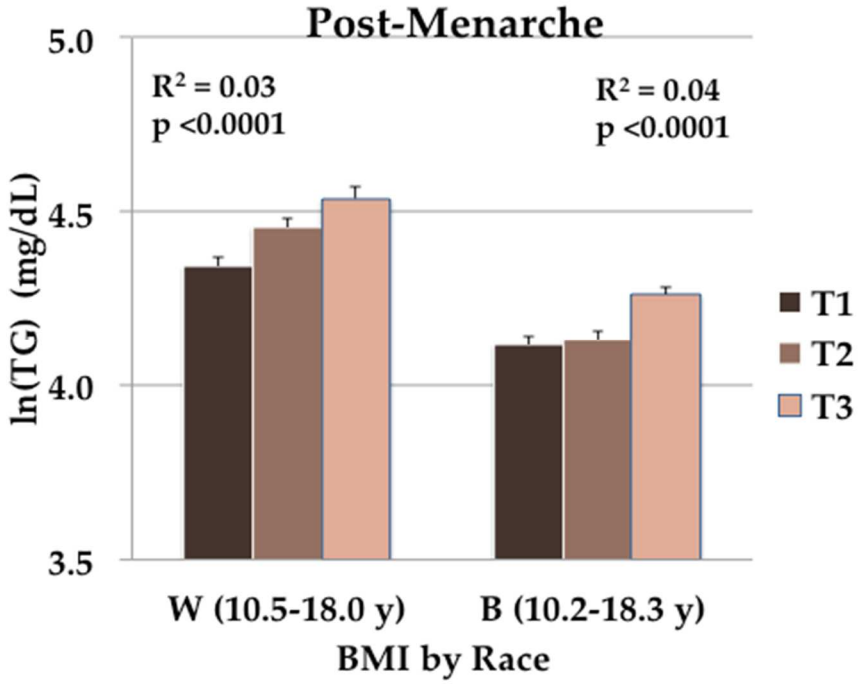
HDL	Pre-Menarche BMI (n=1,237)		Post-Menarche BMI (n=1,351)		Pre-Menarche BMI (n=1,134)		Post-Menarche BMI (n=1,134)	
	W	B	W	B	W	B	W	B
T3-T1	-4.02	-4.50	-4.89	-4.81	-3.74	-4.59	-4.53	-5.37
p-trend	0.0004	<0.0001	<0.0001	<0.0001	0.0013	0.0001	<0.0001	<0.0001
R^2	0.02	0.03	0.03	0.04	0.02	0.03	0.03	0.04

W= white girls; B=black girls

Figure 3.3. TG at 17-20 years (logarithmically transformed) according to Tertiles of BMI, Pre- and Post-Menarche

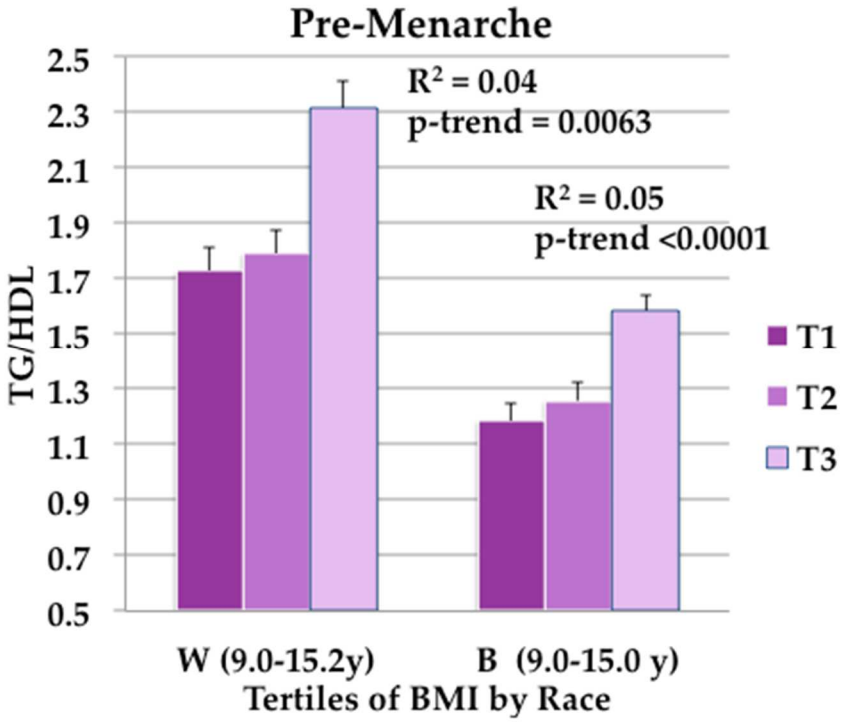


A.

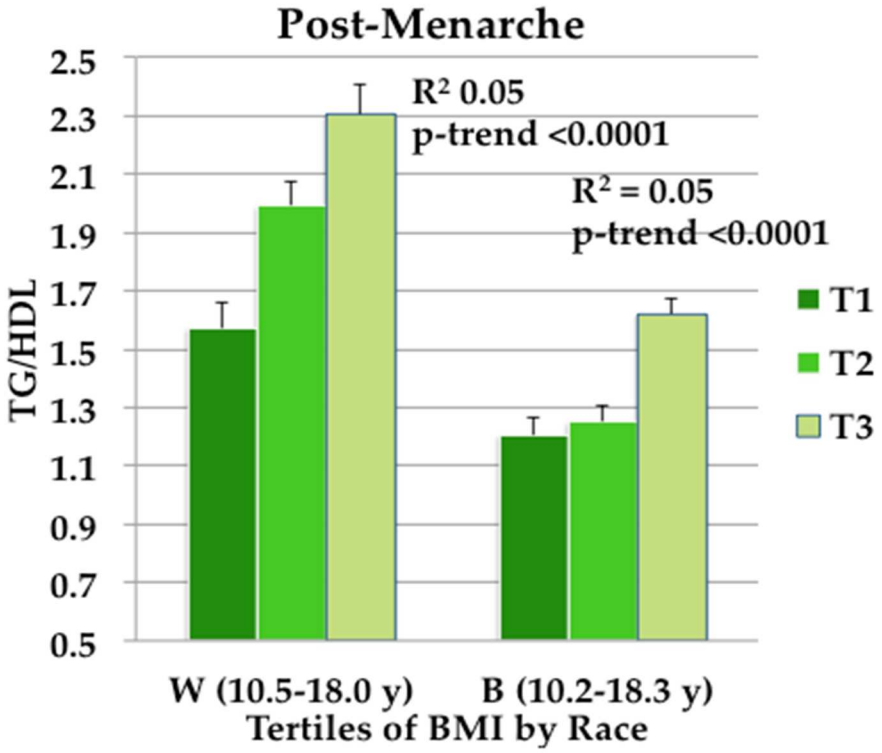


B.

Figure 3.4. TG/HDL at 17-20 years according to Tertiles of BMI, Pre-and Post-Menarche



A.



B.

Subset analysis with and without maternal BMI

While we tested many factors as potential confounders of the relationship between pre-or-post-menarche BMI and later lipid levels, we did find maternal BMI to be a confounder with respect to LDL (in black girls, pre-menarche) and the TG/HDL outcome (in white girls, post-menarche), however we did not present Figures 3.1-3.4 with maternal BMI due to limitations we discuss in the following section. A subset analysis in Table 3.4 compares the effect estimates (T3-T1) of models of TG/HDL presented in Figure 3.4 with the addition of maternal BMI revealed that the addition of maternal BMI slightly strengthened the association of TG/HDL with BMI. In total, the addition of maternal BMI did not significantly change the relationship between **BMI and LDL**: (two-tailed t-test comparison of [Pre-Menarche: White girls: p=0.9592; Black girls: p=0.9226]; [Post-Menarche: White girls: p=0.8697; Black girls: p=0.9170]), or between **BMI and TG/HDL**: (two-tailed t-test comparison of [Pre-Menarche: White girls: p=0.9502; Black girls: p=0.9179]; [Post-Menarche: White girls: p=0.8668; Black girls: p=0.9413]).

Table 3.4. Comparison of Mean Differences in TG/HDL Across Tertiles of Early-Adolescent BMI with and without Mother's BMI

	Without Maternal BMI (Same as model in Figure 3.4)				With Maternal BMI			
	Pre-Menarche BMI (n=1,237)		Post-Menarche BMI (n=1,351)		Pre-Menarche BMI (n=1,237)		Post-Menarche BMI (n=1,351)	
LDL	**W**	**B**	**W**	**B**	**W**	**B**	**W**	**B**
T3-T1	8.10	11.00	11.61	11.34	8.00	9.8	12.00	10.01
p-trend	0.0114	<0.0001	0.0003	<0.0001	0.013	0.0003	0.0002	<0.0001
R^2	0.02	0.03	0.04	0.03	0.02	0.04	0.04	0.04
TG/ HDL	**W**	**B**	**W**	**B**	**W**	**B**	**W**	**B**
T3-T1	0.60	0.40	0.70	0.40	0.60	0.40	0.80	0.40
p-trend	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
R^2	0.04	0.05	0.05	0.05	0.05	0.07	0.07	0.06

3.4. Discussion

In these prospective analyses, both pre- and post-menarche measures of early adolescent body composition were determinants of later lipid levels in both black and white adolescent girls to varying degrees. Post-menarche BMI generally a slightly better predictor of later LDL, HDL, and TG in both black and white girls, although pre-menarche BMI was good predictors of later LDL, HDL, and TG in black girls. In white girls, post-menarche measures reflected more stable trends across classes of body fat, and were also better predictors of later lipids than pre-menarche measures. These results support our findings from Chapter 2 that BMI is a simple anthropometric measure of adiposity in

adolescent girls that may be useful in identifying those who have risk of elevated blood lipid levels by the time of later adolescence. Early adolescent adiposity measures, either pre-or-post-menarche, could provide beneficial information for early screening of associated metabolic risks in adolescents.

Racial differences in lipid levels among pre-and post-menarche black or white adolescent girls are expected. As we observed in Figures 3.2 and 3.3, black girls have higher HDL and lower LDL and TG compared to white girls, which is consistent with racial differences in lipid levels known about adult women(189,190). One study(190) suggests that especially among overweight black women, racial differences in lipids may result in less women making the current criteria for metabolic syndrome and may underestimate cardiovascular risk in black women: this highlights an enduring concern that it may be beneficial to consider screenings based on race-specific criteria for lipid levels, especially with conditions like overweight which may predispose an individual for adverse CMR outcomes. Specifically, Kwiterovich(191) suggests that there is reason to reassess cutpoints for lipids in children and adolescents, particularly among those who are obese. In fact, screening early might be the most important priority to consider to inform future clinical practice, with less emphasis on

cutpoints: a report by Magnussen(192) suggests that using cut points adjusted for each year and sex does not necessarily improve the result of screenings for unhealthy lipid levels.

Body mass index (BMI) is often used in pediatric populations to track risk for overweight and obesity. Further, this study suggests that BMI taken pre-or-post-menarche could be useful as early indicators of later adolescent lipid profiles. BMI is the easiest of the adiposity measures to use, and is commonly used to assess body fat. However, it does not capture body shape or lean body mass well, especially with either genetic (race-related differences in bone density) or other developmental (hormonal changes in body fat deposition) or activity (athletes and elevated lean body mass) differences. While BMI has mainly been used in clinical settings to estimate a child's propensity for obesity and associated metabolic risk, the limitations of BMI are apparent(109). BMI does not capture sources of body fat, particularly depots of visceral adipose tissue that are highly associated with metabolic disease(109). Waist circumference has been proven useful to highlight disparities between black and white adults (112,147). Waist circumference (WC) may add some information about distribution of fat

with respect to clinically relevant metabolic outcomes in developing adolescent girls, and could be considered in addition to BMI for future comparable studies.

A number of studies in children of various backgrounds and ages in childhood and adolescence have compared measures of adiposity, including WC, and different individual or clusters of CMR, such as lipid levels in the context of maturation. Bluher et al. (142)studied obese girls and boys of German/Austrian/Swiss descent, ages 11-18, and the contribution of pubertal development in using anthropometric measures as predictors: their findings revealed correlations between BMI and WC, as well as showed that lipids were more strongly correlated with WC compared to BMI or WHtR, but more so in boys than in girls. Bluher et al. observed that the patterns of body composition association to CMR changed throughout pubertal development, with strongest associations for those individuals who were already pubertal. In a cross-sectional study pre-puberty, Maffeis et al. (146) compared WC to tricep and subscapular skinfolds to explore the relationship between these anthropometrics and lipids, among other CMR, and found WC to be a easy to measure and more easily reproducible way to identify clinically relevant intra-abdominal fat in children than skinfolds. Given findings such as these that show body composition-related

associations with lipid levels, future studies that directly compare BMI to WC as predictors of later lipids in a longitudinal cohort, and in black and white girls, could add interesting insights to our understanding of when and for whom monitoring predictors of lipid profiles could be most useful, given physiological changes that occur during puberty. Since body shape changes in girls around the time of pubertal maturation, examining WC and WHR in addition to BMI before and after menarche could add helpful insights about potential mechanisms, adding to what we know about how adiposity, change in body shape, and puberty may contribute to unhealthful lipid levels.

For those individuals where BMI does not capture a comprehensive view of body composition, measures such as WC, WHR, or %BF may be more helpful early clinical indicators of risk. Insights we provide here may then be suggestions for additional tools to augment BMI screenings and assessment of weight status and obesity-related health risks. WC or WHR measures could still have limitations with introduction of measurement error or measurement of WC inconsistent with those provided in the few guidelines available for adolescent body composition measures. Perhaps in those cases where BMI may not have been a strong predictor of later lipids, it is possible that body shape was still in

flux at the time, as waist size changes during puberty are both an indicator of normal growth, but waist size also could be a prelude for additional risk factors.

Racial differences in early adolescent measures of adiposity and their prediction of later lipids indicate that the risk of more unhealthy lipids in young adulthood is evident. Clinicians may find these results insightful in treating pediatric patients and screening for early signs of overweight and obesity. Our findings about the utility of post-menarche body composition measures is consistent with prior evidence that suggests that lipid levels may change rapidly during menarche, and come to a stable level afterwards(170). Although we cannot conclude which mechanisms may underlie racial differences between white and black girls in how their BMI before or after menarche may predict later lipids, we underline the need for specific clinical tools which may consider race and maturation to identify at-risk adolescents for early interventions and to help them achieve a healthy blood lipid profile.

Possible Mechanisms

Our work may shed light on possible mechanisms for how the relationship between BMI pre-or-post-menarche might reflect adiposity-related

changes in blood lipid levels. We found that measures of body fat can be informative of later lipid levels as early as pre-menarche in black girls. In the case of HDL, this might reflect that there might be a mechanistic or genetic connection between HDL and body fat before maturation hormones and changes influence development, and this might not be as engrained with respect to other lipid risk factors as LDL or TG, for example. Although we did not have biological measures of inflammation, such as c-reactive protein, conceivably, one landmark of excess stored body fat is a pro-inflammatory environment(42,193). Chronic inflammation, particularly, beginning early in childhood and progressing throughout adolescence(194,195), even with additional adverse child environmental experiences(86), may predispose adolescents to development of obesity-related dyslipidemia. An inflammation hypothesis could reflect the actual inner state of metabolically active visceral fat depots that may be associated with higher circulating lipids. Our findings about TG/HDL suggest that as a proxy for lipid particle size(154), TG/HDL may be informative to assess risk of dyslipidemia and associated cardiometabolic risks related to lipid particle size (such as insulin resistance(185)) in white girls. White girls already have higher TG, and to understand the implications of this racial difference, TG/HDL could be an interesting target to consider when thinking about a mechanism for

dyslipidemia in adolescents, and in particular, prevention of an atherogenic or insulin-resistant lipid risk profile in white girls. Black women are also known to be more insulin-resistant than white women, however, a hypothesized marker of lipid particle size associated with IR, higher TG/HDL, was not higher in black girls. It is possible that TG/HDL may not be a very informative marker of insulin resistance in adolescent girls, or that there may be other mechanisms of insulin resistance apart from those that operate through regulating lipid particle size, which confer IR.

Interrogating the associations between body fat and cardiometabolic risk to see if early, pre-adolescent measures can predict racial differences(121) in different risk factors, specifically in later lipids could be a useful starting point to understand novel possibilities for the development of high blood pressure and insulin resistance. Excess circulating lipids may act on the architecture of arterial walls, for instance, to elevate blood pressure or deteriorate blood vessels, resulting in diabetic complications. The relationship between puberty and insulin resistance has been previously explored(117), however, we expand upon this idea of link between puberty and cardiometabolic risk factors to test specific ranges around age of menarche and to compare and suggest when these values

of early anthropometric measures of body composition, and which ones, are best to predict later lipids.

Prediction of TG/HDL using early anthropometric measures of body composition could provide useful surrogate information about lipid particle size and density of circulating blood lipids, and inform insights about potential mechanisms for the better early detection of future coronary artery disease. Some studies suggest that TG/HDL is an indirect predictor of insulin resistance(196–198) and others associate it with risk myocardial infarction in adults(184,187,199,200). While a number of groups are trying to understand the relationship between TG/HDL as an indicator of lipid particle size and cardiometabolic outcomes(183), at this time there is a lack of clear agreement around meaningful TG/HDL cutoffs that are definitively associated with other metabolic risks - specific atherogenic risks, or the implications of different lipoprotein sizes, although more has been studied with respect to healthy TG/HDL levels (under 2) among in different populations who are insulin resistant(188,201,202).

We found that TG/HDL seemed to be an interesting marker among white girls, both pre-menarche and post-menarche: increases in early WC predicted increases in TG/HDL above 2: in the highest tertile of WC pre-menarche TG/HDL and post-menarche TG/HDL=2.32. Interestingly, one research group studied TG/HDL and its relationship to insulin resistance in pre- and post-pubertal children(203), finding a strong association between TG/HDL and insulin resistance in children, along with higher BMI, WHR, blood pressure, and a more atherogenic lipid profile. While we were not able to extend our findings to examine the insulin resistance in our study, that could be a natural extension of this work given the growing literature around TG/HDL and insulin resistance.

Excess body fat during childhood and adolescence and later cardiovascular related outcomes may intersect in adolescence around maturation. But, it is not certain whether the effect on adult obesity associated with increases in pre-menarcheal BMI are due to the influence of childhood obesity on both menarcheal age and adult obesity, rather than due primarily to menarche age. The Bogalusa Heart Study estimates that 60-75% of adult obesity is due to the effect of child obesity on both menarche age and adult obesity(204). Lifestyle factors may result in early menarche, including stress, exercise, or diet,

initiating maturation-related processes with hormonal and body composition changes earlier than normal(205). Another study in the NGHS cohort found that early or late menarche were risk factors for adult oligomenorrhea, metabolic syndrome, and cardiometabolic abnormalities such as diabetes and polycystic ovary syndrome(115). Some also address the biological impact of hormonal changes around menarche during the pubertal transition, finding that changes in leptin closely followed peri-menarcheal changes in %BF. As a hormone involved in regulation of hunger and satiety, it is interesting that this hormone rose closer to menarche than insulin or other sex hormones(206).

Age of menarche itself has been recognized as a sensitive indicator of physical, biological, and even psychological environment(207): as the trend for menarche age and puberty onset is earlier, it could be a thermometer offering a reading of the most pressing stressors influencing physical and changes in metabolic risk in populations. Although what is uniform and considered normal maturation differs among adolescent girls, more studies with a longer follow-up are needed which could more easily study the mechanisms for obesity-related increases in dyslipidemia risk during pubertal development.

Strengths

We contribute data from a large biracial cohort to this body of knowledge in the hopes of strengthening our understanding of possible causes of disparities in health vulnerabilities in adolescent girls. We hope that this work will expand the useful criteria for early assessment of cardiometabolic risk and highlight the integrated way that many biological, environmental factors interact to increase the overall cardiometabolic risk of a developing child. In the Newton Girls Study, girls who were overweight before menarche were 7.7 times more likely to be overweight as adults, and early menarche did not further elevate risk(180). They suggest that the influence of early maturation on adult female overweight could rather largely be a result of the influence of increased relative weight on early maturation(124). Previous studies have not accounted for the possibly distinct role of maturational timing and development in the longitudinal prediction of dyslipidemia-related outcomes in black and white girls, which we discuss here. In addition to consideration of menarche age in later dyslipidemic risk, in situations like ours in which collected data from the cohort were insufficient to study risk of insulin resistance in depth, having an example of a new potential angle by which to look at insulin resistance risk involving lipid

particles and their size by looking at the triglyceride to high density lipoprotein is an interesting concept.

Limitations

The results of these analyses are limited to females and the conclusions reflect trends in black and white girls only. Our findings are limited to a comparison between black and white girls; differences we saw here cannot be generalized to girls of other races, including Hispanic or Southeast Asian girls who may also be at risk for cardiovascular health outcomes. Differences in activities that young people do today due to cultural changes may alter the effect of potential confounding factors such as activity or television on body weight and body composition. Further, the results we report here that relate to menarche age cannot fully incorporate any interaction effect on metabolic risk due to genetics from the mother's age of menarche and the daughter's age of menarche, as few other markers from the mother are available in this data set which could reflect the potential role of shared genetics in risk development. In our analysis, maternal BMI was related with later lipids and adiposity in a couple of instances (with LDL and TG/HDL) as a confounder. Maternal BMI could meet the criteria for an independent association as a predictor of later

lipids through shared genetics. A mother with a high BMI could have a risk profile of a heavier parent with dyslipidemia herself. Or, mother's BMI could reflect a shared environment or lifestyle with her daughter that affects daughter's BMI. The maternal BMI variable could be a combination of genetics and environment, and other longitudinal cohort studies that might perform a study similar to ours, but with biomarkers for the mother that give information on her metabolic health could help answer this question. The R^2 are notably low: this makes sense because of the subgroups of our sample in which we perform these analyses, where it is reasonable that the detectable levels could be lower compared to that which might be observable in the large population. Further, while the NGHS population our study sample is sourced from does include many who have elevated LDL or TG, and lower HDL levels (171), it is possible that since most of the girls do not have unhealthy lipid levels, if we were to examine the same question among girls who are obese, or those who have high genetic risk for other reasons, the results might show a stronger R^2 and relationship between BMI and lipid levels. It is also true that certain measures may not lend themselves to being predicted statistically with a high degree of R^2, adding to the importance of sharing this work in the context of the larger

literature on early adiposity prediction of later lipid outcomes among adolescents.

While menarche age provided some important insights about optimal time to look at body fat predictors in adolescent girls, there could be potential challenges with implementing menarche age in future models of dyslipidemic risk. Classification of girls by menarche status at the time when her waist circumference was measured may bring in error due to self-report of their age of menarche. For example: some girls may not understand the concept of menarche clearly, and may answer differently in different exam years. Corroborating their self-reported responses with that of a parent or guardian and a physical exam could, however, ensure consistency in reporting of menarche age.

Conclusions

This work advances the field by showing evidence that BMI, as a simple anthropometric measures of body fat BMI in early adolescence, as early as 2 years pre-menarche, is a predictor of lipid profiles. Our findings indicate that BMI may predict later lipid levels that are biomarkers of dyslipidemia, which if identified early, could prevent development into associated cardiovascular

disease. Pre-menarche body fat, for instance, could be useful to predict HDL levels as a marker of metabolic risk in young black girls. Girls who are identified as high risk based on simple anthropometric screenings of body fat could be monitored and put on early lifestyle interventions by their clinician. Lipid profiles and other dietary of behavioral attributes could be monitored and prevented from the age of 9 instead of dealt with in treatment. We recommend screening for body fat using simple, cost-effective, age, race, and maturation-stage appropriate tools as early as possible during adolescence for the prevention of dyslipidemia. While a guideline that is this specific does not exist, we do hope to bring awareness to pediatric care providers about early, detectable differences in risk. Early identification of later adolescent lipid levels through simple, non-invasive methods holds great value for early prevention of later risk of serious chronic disease in adult women.

CHAPTER FOUR: The contribution of maternal socio-behavioral risk to daughter's change in BMI throughout adolescence

4.0 Abstract

To address the limited evidence base for the role of maternal depression in child obesity, we studied the relation between exposure to maternal depressive symptoms among 9-10 year-old girls and change in their body mass index (BMI) throughout adolescence, as well as their BMI at age 18. Previously collected data for 1,257 girls enrolled in the NHLBI's National Growth and Health Study who had complete information on maternal depressive symptoms at baseline (when girls were 9-10 years of age), BMI at the end of follow-up (at 18 years of age), and all potential confounders of interest were included in the NGHS sample used in these analyses. Mothers completed a depressive symptom questionnaire modified from the Zung depression scale. Scores ranged from 9 to 39 (with a theoretical maximum of 40 points) with higher scores reflecting greater depression. Sensitivity analyses were used to explore the classification of maternal depressive symptoms. Final categories were low (<22), moderate (22-26), and high (≥26) levels of depressive symptoms. Firstly, mixed linear regression modeling was used to explore the relationship over time between maternal depressive symptoms and the change in child's BMI during

adolescence. Nine to ten year-old daughters of mothers with the lowest depressive symptom scores maintained the lowest BMI levels throughout adolescence and those whose mothers had the highest depressive symptom scores had the greatest increases in BMI ($p<0.05$). We presented models of maternal, dietary, psychosocial, demographic, and family mealtime variables that may help explain the observed relationship between maternal depressive symptoms and later adolescent BMI. Of these, we evaluated socioeconomic status, child's self worth, and television watching behavior as potential effect modifiers of the relationship between mother's depressive symptoms and daughter's late adolescent BMI: the combined effects of higher TV watching, lower self worth, or lower SES on daughter's BMI among those with mothers with higher depressive symptoms were all significant ($p<0.0001$). Multivariable modeling, adjusted for race, demonstrated that the combined effect of television watching with exposure to maternal depressive symptoms proved to be an important predictor of late adolescent BMI ($p=0.0053$). Next, we explored the question of whether intermediate effects of adolescent psychosocial factors, such as childhood depression or self-esteem, explained these findings. A child's sense of self-worth may operate on the pathway mediating the effects of exposure to maternal depressive symptoms in early adolescence on later adolescent BMI:

higher self-worth may be a marker for internal resilience that could buffer stressful effects of maternal depressive symptoms. Maternal depressive symptoms are a risk factor for increases in daughter's BMI throughout adolescence. Factors such as child's depression, child's early adolescent BMI, and maternal BMI partially, but not completely, explain this effect. These findings address an important gap in knowledge concerning the impact of exposure to maternal depressive symptoms during childhood on increased late adolescent BMI preceding the development of obesity. Maternal depression is a risk factor for daughter's increase in BMI during adolescence.

4.1 Background

Stressors at Home: Sources of toxic stress have far-reaching implications for health risk

The potential link between psychosocial stress in childhood and long-term effects on adult cardiovascular disease risk has garnered recent attention(76). As many predictors of cardiovascular disease also have their roots in childhood, the extent to which early experience of psychological distress may impact long-term effects on later health and wellbeing requires further investigation(77,78). Childhood eating behaviors(16–18) are shaped by socio-environmental factors in the home(19,20). It is important to consider not only how children eat, but what

they eat: eating behaviors predict nutrition and diet quality(19,21) and are associated with later development of obesity risk(20) and chronic diseases. These eating behaviors are usually first learned within the home and in the socio-environmental context of the family(11,17,22) during family meals(23–25). While the home can be a safe and supportive place, in certain families who face social or economic stressors(26), the home can also be a source of tremendous stress during developmental periods(27) wherein children learn how and what to eat(28–31). We examine the relationship between maternal mental health and child BMI within a prospective cohort to look at evidence of the potential long-term effects of exposure to maternal depressive symptoms on the BMI of their adolescent daughters.

Maternal depression(60–63) may be a specific source of toxic stress in the home. Maternal depression symptoms are a psychosocial risk factor which is widespread in the United States(26,36,58,59). Further, women of low SES and from certain ethnic minorities may have fewer resources with which to cope with adverse life events(26); such women also exhibit the highest rates of maternal depression(60–63). Depressed mothers are often unable to buffer family stressors and to supply a supportive child-adult relationship that is involved and

responsive. Toxic stress is the most dangerous form of stress response resulting from frequent or prolonged activation of the body's stress response systems without the buffering protection of a supportive adult relationship(69).

Socioeconomic status (SES) and parental education are two family resources that shape the environment of growing children and have been more extensively studied. The theory behind the effects of social and environmental factors on child weight status is well-established(16,22,32–35). SES may additionally act as a stressor that adversely influences mental health of maternal caregivers in a way(60,67,68) that challenges the social and emotional bond between mothers and their children. Obesity has not been studied in the context we propose, investigating potential pathways predicting child BMI in the context of exposure to toxic stress from maternal depressive symptoms, in combination with potential intermediary factors of family meals and lifestyle factors.

It is also possible that toxic stress may affect the quality of food presented at family meals, and thus modify BMI, so it is important to look at the role of diet. Proper nutrition and dietary patterns(91–93) - including nutritional content, diet variety, and diet diversity, as well as physical activity are among the lifestyle

behaviors which are associated with well-being(94). A lack of a mother's capacity to guide the healthy development of eating behaviors in their children(58,135) during family meals(22,25,73,136) may contribute to a cumulative effect of toxic stress. Toxic stress from compromised maternal mental health may predict obesity in children(72) via action on family mealtime practices(20,73,74) and childhood diet quality(21,75) (see Figure 4.1).

Television viewing is a lifestyle behavior that is associated with increased BMI. One study tested if TV viewing has concurrent effects on BMI, and also investigated if current TV viewing exerts long-term effects on future levels of TV watching. As might be expected, the frequency of past behaviors is a standard indicator of habit strength and likelihood of the behavior to continue into the future(208). The content viewed may also influence diet and eating behaviors through high calorie snacking inspired by advertisements. The authors concluded that heavy childhood TV watchers tend to become heavy young adult TV watchers and that this viewing behavior from childhood to young adulthood independently increases BMI(209). The role of child's TV watching in influencing child BMI has not been studied in families with mothers who have depressive symptoms. Understanding if TV viewing and maternal depression may exert

combined impacts on child health, and the extent to which this may occur, is an important evidence gap to address.

Maternal Depression and Child Health

Prior cross-sectional work in the area of maternal feeding practices and effects on child weight status and obesity has focused on early years(103,104). Studies of the effect of stress on child overweight consider ways in which parental stress may be transmitted to children through mechanisms of diminished parenting, lack of time with children, or inability to shop for or cook nutritional foods. A cross-sectional study of children ages 3-17 (210) found a link between parent-perceived stress and diet, specifically child-fast food consumption, which is an important behavioral indicator of obesity risk, and saw a direct association between total parent stressors and child obesity. One study in NHANES(64)assessed maternal stressors, including mental, physical, financial, and family structure ones, which have been linked to health outcomes for children, particularly in low-income families. The principal finding of the authors supports the idea that maternal stressors have a profound impact on childhood overweight: they found that younger (3-10 year old) children in food secure, low-income households who experience greater levels of maternal

stressors have a greater likelihood of being overweight than food insecure children. However, little is known about any enduring effects of maternal depression on adolescent health(58). As a large cohort of girls followed prospectively throughout adolescence, NGHS provides useful data about both maternal depressive symptoms and health during this critical period(70) of adolescence.

Exposure to childhood adversity is associated with obesity(81), however the contribution and mechanisms of exposure to maternal depressive symptoms to child obesity is not understood. A meta-analysis of 41 studies with 190,285 participants demonstrated that childhood maltreatment was associated with development of obesity risk over the life course (odds ratio=1.36, 95% CI: 1.26-1.47), although it was insignificant in studies focusing on emotional neglect or adjusting for current depression. Maternal and child depression(211,212) may also be closely related such that mothers who report symptoms may have children who report depression over longitudinal follow-up. In NGHS, using the Center for Epidemiological Studies Depression Scale (CES-D) at ages 16 and 18, adolescent depressive symptoms were associated with elevated BMI in young adulthood (ages 21-23), and especially in black girls(88). Other studies that did

focus on the child's own psychological state (as opposed to association with exposure to mother's mental health symptoms) found associations between phobia, panic, anxiety, or depression disorders and later obesity(88), but did not explore other contributors to intrinsic psychological wellness such as the child's sense of self-worth. Studies that assessed adversity in childhood or adolescence examined influences of peer bullying, or abuse or neglect at home(85–87,96–102), and have not focused on maternal depression and adolescent BMI. Healthy social relationships, such as those in a family, which may build self worth can buffer against adversity and support positive health(90).

Disparities in Child Obesity Risk

Children of different races and socioeconomic statuses experience disparities in obesity risk(2,13–15) and must continue to be a focus of nutrition research to inform the targeted interventions that best-serve these at-risk populations(134). Another important disparity is that adverse experiences of stress that impact obesity manifest in women more so than men(81), warranting further study of maternal stressors.

Evidence Gap

Little is known specifically about any enduring effects of maternal depressive symptoms on adolescent health(58). The mechanisms for the effect of Adverse Childhood Experiences, including exposure to maternal depression, are not very well understood. Perhaps part of the reason for a lack of psychosocial risk factors in evidence was pointed out in the 2017 American Heart Association statement: uncertainty over whether ACEs exert a dose-response(79,89,213–217) or threshold effect(218), combined with uncertainty over the best, standardized method to measure ACEs(80) point out a clear need for more prospective studies like ours that include ACEs in prediction of CMR. Particularly, the independent, long-term effects, if any, of maternal mental health as a predictor of the outcome of obesity risk in a study sample of black and white adolescent girls of varying levels of socioeconomic statuses are not known.

Longitudinal studies over the life course that do not rely on retrospective data would be powerful in identifying important, modifiable targets within the family and environmental context to prevent child obesity. Despite variations in definitions of CMR clusters and risk, a review of studies of CMR risk factor clusters indicate that risk factors are fairly stable from childhood to adulthood

and suggest that early interventions in identified high-risk children may be profitable to decrease likelihood of CVD outcomes(46). Maternal depression is a source of toxic stress linking experience of toxic stress in childhood to child obesity and elevated cardiometabolic risk factors as young adult women, and the effect likely differs between black and white girls. We aim to estimate the effects of maternal depressive symptoms, on change in BMI among adolescent girls and further, to determine whether these effects are explained by or modified by factors such as the child's self-worth or depressive symptoms.

Figure 4.1. Conceptual Framework for Chapter 4

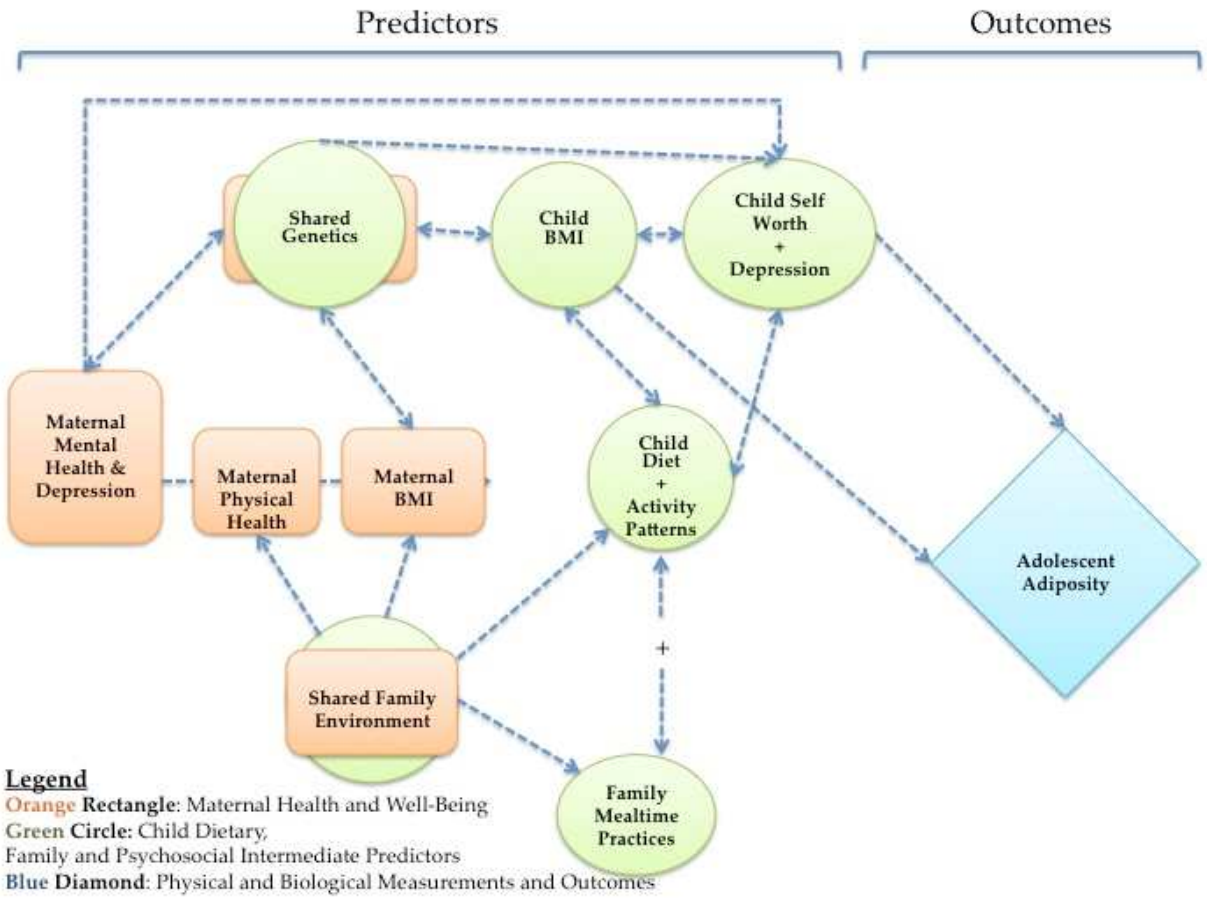
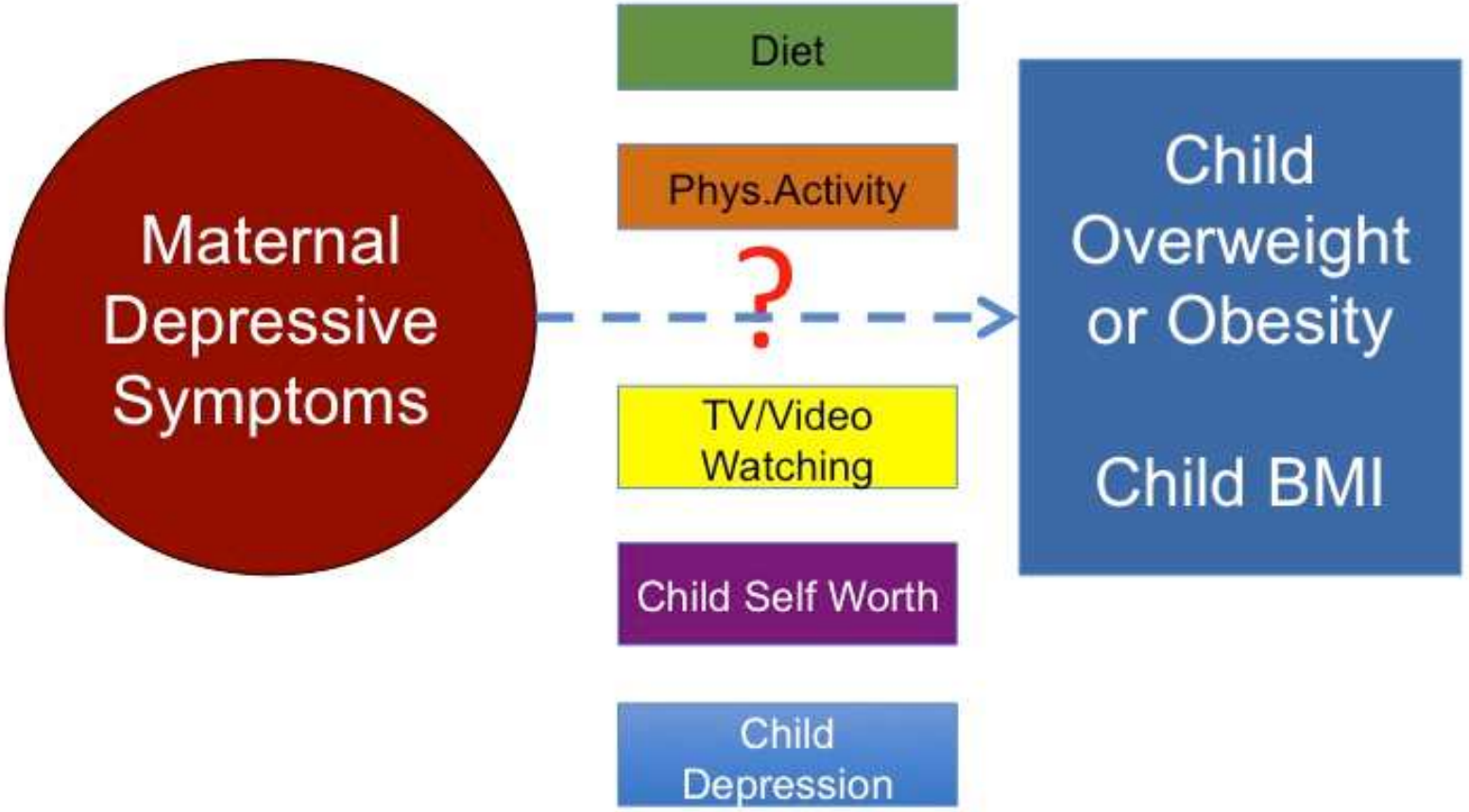


Figure 4.2. Exploring Possible Mechanisms



4.2 Methods

4.2.1 Study Population

Data from the National Heart Lung and Blood Institute's Growth and Health Study (NGHS) was used for this study. Study participants in NGHS were recruited from three separate geographic areas to minimize the likelihood of biased results due to regional differences and to allow for comparison across socioeconomic backgrounds. Subjects were recruited from census tracts that had approximately equal black and white residents and the least disparity in education and income(122). Children were enrolled from three clinical centers: the University of Cincinnati/ Cincinnati Children's Hospital Medical Center in Ohio, Westat, Inc./Group Health Association in Rockville, Maryland, and University of California at Berkeley, in Berkeley, CA and were followed prospectively for 10 years. Berkeley and Cincinnati girls were recruited from public and parochial schools, and those from Westat were recruited from a health maintenance organization. The criteria for the selection of subjects and broad exclusion criteria from the original cohort have been previously described in detail(116–118). Research protocols were reviewed and approved by the NHLBI's Institutional Review Board. Measurements of body fat and related cardiovascular disease risk factors were evaluated according to study protocol at

annual exams by examiners who were certified, monitored, and retrained to use the NGHS protocol. The original study investigated the development of obesity in black and white girls during adolescence and studied the environmental, psychosocial, and cardiovascular disease correlates that may explain the higher risk of cardiovascular disease in black women. The analyses were performed in two subsets of black and white girls (1,487 for mixed linear models; 1,257 for multivariable linear models) with complete data for all exposures, outcomes, and covariates.

Eligibility Criteria: In brief, girls eligible for recruitment had to be a) within two weeks of age 9 or 10 at the time of the first clinic visit b) had to self-define as black or white and come from racially concordant Caucasian or African American households, and c) parents had to complete a household demographic form, give parental consent and the child also gave assent for participation in the study.

Study Selection Criteria: Mixed linear models of the relationship between maternal depressive symptoms and daughter's BMI throughout adolescence included 1,487 girls who had complete data for their mother's maternal

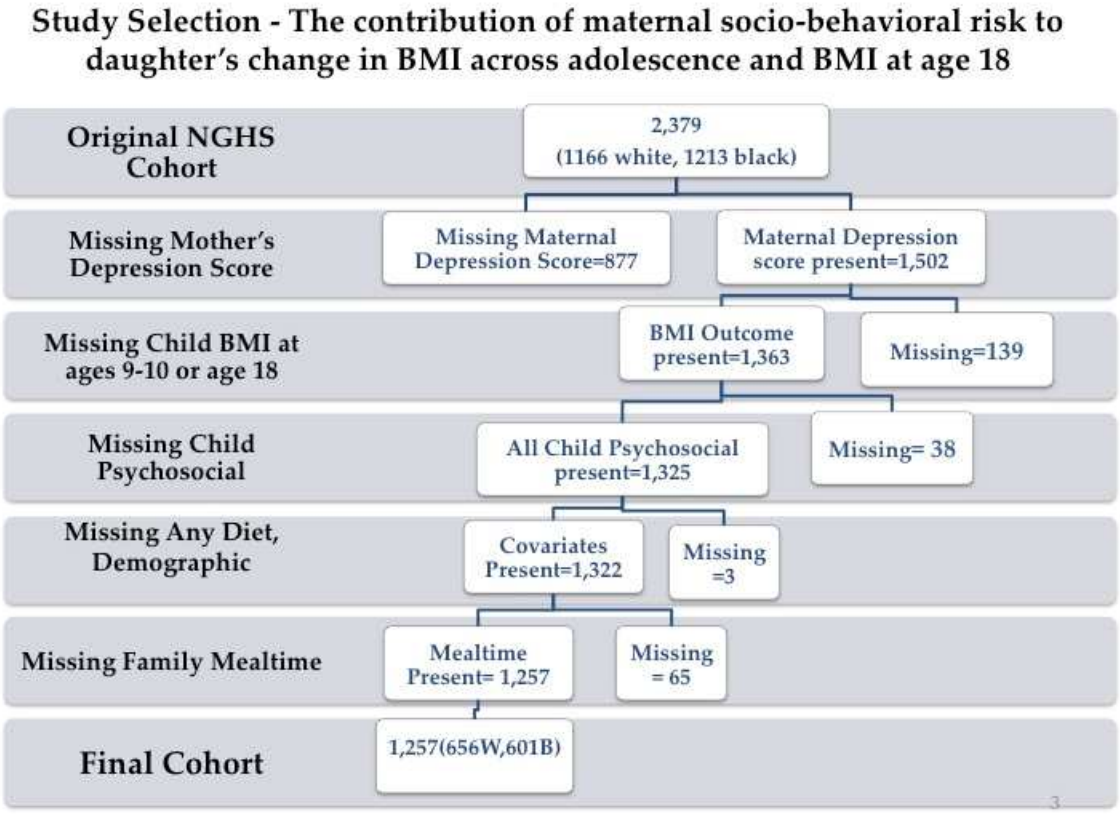
depressive symptom score, all potential covariates of interest at each age, and girl's BMI at each age: 2,330 had covariates at each age category, and out of those, 1,502 girls had maternal depressive symptoms score. Limited dietary data was available for 15 of those girls, leaving a total of 1,487 girls who had complete data.

The multivariable linear analyses examining the contribution of maternal depressive symptoms to late adolescent BMI included girls with complete data (n=656, white girls; n=601, black girls) for the exposure of mother's depression score, the outcome of child body mass index [BMI] at age 18, child depression and self-worth scores, and potential confounders of interest (baseline height and body mass index at ages 9-10; menarche age; socioeconomic status; physical activity, servings of whole grains, percent of energy from discretionary fats, added sugars, percent energy from saturated fat [averaged from ages 9-17]; family and family mealtime variables at the start of the study of family meal (yes/no), length of the evening meal, importance of family to the child).

We compared the subjects who were included with those who were excluded and there was no large or systematic difference between the two

groups. For example, the included subjects have a slightly higher HEI score than the excluded subjects (44.5 ± 7.3 vs. 42.9 ± 7.0) while the opposite was true for activity levels (20.1 ± 10.0 vs. 20.4 ± 11.2).

Figure 4.3 Study Sample Selection Tree



4.2.2 Exposure Variables

The socio-environmental construct of toxic stress in the NGHS cohort reflects maternal depressive symptoms, including 8 variables of maternal self-

report of depression, anxiety, trouble getting up in the morning, crying episodes, irritability, tiredness, trouble falling asleep, and anger. These maternal depressive symptoms are based on the Zung scale(219) created to evaluate the presence or absence of depressive symptoms in a simplified manner compared to prior evaluations. Subjects rated their experience of these factors according to frequency *(never, rarely, sometimes, often, always).*

Creation of Maternal Depressive Symptom Score

The above-described eight variables were combined into a total score, ranging from 0-40, where higher scores indicated a greater presence of maternal depression symptoms. Based on their score, subjects were classified into a depressed (score of 26 to 40), moderately depressed (score of 22-26), or not depressed (score of less than 22) group. Mothers in our study were limited to the 94% of the total mothers in the study who were natural mothers – others were other female relations. Sensitivity analyses were performed to optimize the constituents in each of the low/moderate/high depression groups. We evaluated maternal depressive symptoms as a type of toxic stress exposure with respect to the outcome of late adolescent BMI in their daughters.

4.2.3 Outcome Variables

We used the categorical exposure of maternal depressive symptoms with a *continuous* measure of the daughter's obesity averaged over pairs of ages (e.g. 9-10, 11-12, etc.) and at age 18.

4.2.4 Potential Confounding Variables

Potential confounding variables fell into these categories: demographic, anthropometric, dietary intake and eating patterns, physical activity records and patterns, psychosocial measures, beliefs and attitudes about certain aspects of health, body satisfaction and family influences. Upon verification, there was no confounding by diet, activity, or family meal variables.

Demographic Factors

Age was the exact age calculated based on the child's date of birth. Race/ethnicity was self-declared and collected at study entry. Categories of socioeconomic status (SES) were created by combining data on income and education as follows: (a) low - household income < $10,000, regardless of education level or household income from $10,000 - <$20,000 and education level

of high school or less; (b) moderate - household income $10,000 - <$20,000, household income $20,000 - <$40,000, regardless of education, or household income $40,000 or more with only a high school education or less, and (c) high - more than a high school education and an income of $40,000 or more.

They were measured according to detailed methods for collection which are described elsewhere(116,124,137). Out of all the potential predictors or confounders, the only confounder we found was average television or video viewing over adolescence, which may reflect a sedentary lifestyle.

Dietary Factors

A wide range of dietary variables was measured and available for use. Diet was assessed in 8 of the 10 total yearly exam visits (at years 1,2,3,4,5,7,8, and 10) using a 3-day food diary including two weekdays and one weekend day. To complete the diaries, girls were given instructions by registered dieticians and provided with a set of measuring cups, spoons, and a ruler along with a binder of illustrated instructions on how to record portion sizes for their food intake using household measures. Three-day food records were used to record dietary

intake, and after these were completed, nutritionists interviewed the girls to verify the entries.

Food records from 2,147 (86% of the black girls, and 95% of the white girls) out of 2,379 girls enrolled in NGHS at baseline were received. To analyze the nutrient content reflected in these records, they were entered into the University of Minnesota's Nutrition Data System (NDS)(156). The NDS system estimates daily intake of nutrients based on these food records. Servings of USDA-defined food groups (157)were derived from the NDS output by linking ingredient codes with food codes from the USDA's "MyPyramid Equivalents Database". Together, this provided each subject's nutrient intake along with intakes in all USDA food groups and subgroups, including but not limited to total energy, carbohydrates, protein, fat, dairy, fruit and vegetable, whole grain, and fiber. Average intakes from ages 9 to 17 were used in our analysis, where at least two sets of dietary data were required to be present for this average. Food records were used to calculate scores for the Healthy Eating Index 2015 (HEI-2015) and Dietary Approaches to Stop Hypertension (DASH) diet scores. The HEI-2015 score includes 13 dietary constituents in the following categories: total fruit; whole fruit; total vegetables; legumes; whole grains; dairy; total protein

foods; seafood; eggs; soy products; nuts and seeds; refined grains; saturated fatty acids; polyunsaturated fatty acids; monounsaturated fatty acids; sodium; calories from added sugars; and total calories. The DASH eating plan recommends foods high in potassium, calcium, and magnesium, protein, and fiber and lower in sodium. The DASH score represents consistency with the DASH diet and includes components in the following categories: dairy; meat, poultry, fish, and egg; whole grains; vegetable; fruit; nuts, seeds, legumes, and a total score calculated as previously described using criteria for NHLBI food intake recommendations(220).

Physical Activity and Television

Physical activity was assessed during administered structured interviews in study years 1,3, and 5 and then self-administered for years 7-10 where activity was measured by self-report in a Habitual Activity Questionnaire (adapted from Ku et al.(158)) that described exercise patterns of the last year(159). Standardization and optimization of data collection on physical activity in NGHS was established during year 7 of NGHS at the University of Pittsburgh's Physical Activity Resource Unit. To combat possible literacy limitations by children in the first study visit, physical activity was measured using a pictorial menu of

activities that children commonly do. Waking and sleeping times were recorded within each of the three, 24-hour entries and duration for activities included 1-15 min, 16-30 min, and >30 min. Activity from physical activity classes, sports in the school year or summer, summer physical activity, and activity in the rest of the year were summed for an overall physical activity score. The HAQ score in MET-times per week in each of these categories was computed by multiplying the MET (metabolic equivalent, the ratio of metabolic rate during a specific physical activity to a reference metabolic rate, where 1 MET = 3.5 ml 0_2 kg^{-1} min^{-1} in MET/min/day) scores for activities by weekly frequency, and a fraction that reflected if the activity was completed during "most", "half" or a "small part" of the designated time of the year from the activity diary(160,161). These summary scores were modified from those used in adult studies to reflect energy expenditure commonly associated with those activities for a given age and gender over the whole past year.

Television (TV) or video hours in half hour increments were collected in two ways: 1) hours usually watched were collected using a reference directory of specific programs (study years 1,3,5) updated annually, and 2) by report of TV hours usually watched (study years 6-10) during the morning, afternoon, and

nighttime hours of a typical week (161). In a methodological test in the first exam, a subset was asked both for program watched, and number of hours of TV movies or videos watched in the past week and found data captured from programs watched was initially more accurate. Average physical activity METs and TV or video watching hours per week over ages 9-17 was used in our analysis.

Child Psychosocial Factors

Child self-worth score was derived from the Global Self-Worth Scale (Harter Self Perception Profile Score), collected at study years 1,3,5,7,9. The child self-worth score assessed the child's self-esteem with six questions asked using a child scale in years 1 and 3, and five questions asked in years 5,7,9 scored an adolescent scale. For the five questions, there were two questions asked for each of the 4 scales. The scale included parameters to assess scholastic competence, social acceptance, athletic competence, physical appearance, and behavioral conduct. The range of scores for self-worth was 1-4.

Child depression was measured in years 8 and 10 of the study(88) using a 20-question scale, the Center for Epidemiologic Studies Depression Scale, or

CESD(221), the gold standard measure for depression,. The questions asked were: I was bothered by things that usually don't bother me; I felt that I could not shake off the blues even with help from my family or friend; I felt that I was just as good as other people; I had trouble keeping my mind on what I was doing; I felt depressed; I felt that everything I did was an effort; I felt hopeful about the future; I thought my life had been a failure; I felt fearful; my sleep was restless; I was happy; I talked less than usual; I felt lonely; people were unfriendly; I enjoyed life; I had crying spells; I felt sad; I felt that people disliked me; I could get going. For each question, children could select from the following responses for a score for each question: rarely or none of the time/less than 1 day; some or a little of the time/1-2 days; occasionally or a moderate amount of time/3-4 days; and most or all of the time/5-7 days. The CESD is a continuous variable and the range of scores is from 0-53.

Family Mealtime Factors

Numerous forms asked questions of the girls about variables concerning mealtimes and preparation of food, as well as variables that reflected cohesion within the family. This included a categorical variable for how important family activities are to the child with response categories of: from very important,

important, unimportant, and very unimportant. Whether or not the girl's family ate meals together was scored as yes or no. Relative length of the evening meal was scored as: <10 min, 10-20 min, 20-30 min, and >30 min.

Maternal Factors

Parents provided data at study years 1,3,5, and 7. Biological mother's BMI was collected, at study years 1,3,5 and 7. The first available of these was selected as the mother's BMI in our analyses, with most deriving from study year 1. Mother's age at first period was ascertained by questionnaire at study years 1 and 3.

4.2.5 Statistical Analyses

Our objective was to first estimate the effects of maternal depression on BMI among adolescent girls at ages 18-20 years, and secondly, to determine whether these effects are explained or modified by intermediate factors such as the child's self-worth or depressive symptoms, maternal BMI, TV viewing, SES, or the child's early adolescent BMI (Figure 4.2). The maternal depressive symptom exposure was treated as a categorical variable with low, moderate, or high levels of maternal depressive symptoms as described in section 4.2.2. The

outcome (BMI at 18-20 years) was treated as a continuous variable. Statistical analyses with mixed linear regression modeling and repeated measures multivariable linear models were performed using SAS 9.4.

Preliminary Modeling

We examined more than 40 variables as potential confounders, and then excluded those that were highly correlated with one another and could not be modeled together. We tested potential psychosocial factors that may mediate the effect of toxic stress or family meal patterns with late adolescent BMI. These include the child's sense of self-worth derived from the validated Harter Scale of Self-Worth(222) and also her perception of family cohesiveness, which includes using a validated family cohesiveness scale, FACES III. Variables examined included child depression, maternal risk factors; child involvement in meals; parental involvement in meals; stress, anxiety, worry, family cohesiveness, child self-worth scales; rules around eating; and parental perceptions of their child's eating habits. The correlation between the maternal depressive symptoms and family meal pattern constructs, child self-worth scale, and family cohesiveness scale were ascertained using Pearson Correlations for continuous variables. Additional variables of interest related specifically to the context of family

mealtimes, including parent and child perspectives on nagging, rules around at mealtimes, snacking and mealtime habits were predictors of later obesity were among those we examined as well.

After breaking remaining variables up into clusters of factors customarily associated with obesity, child's diet, family eating behaviors, and psychosocial ones, we systematically tested each factor independently and in combinations; we first examined possible effect modification and confounding using mixed linear modeling, and then secondly, we confirmed our conclusions about confounding and examined possible causal intermediates using multivariable linear modeling. Using these strategies, we selected and retained variables that demonstrated a significant relationship with both maternal depressive symptom score and child BMI at age 18 in our final mixed linear models. With the schematic of Figure 4.2 in mind, we modeled TV, physical activity, HEI-2015 (average from 9-17 years), DASH (average from 9-17 years), SES, child depression (at exam 10), family meal together (at exam 1), and child self worth (at exam 1) with the maternal depressive symptom exposure, and then separately explored how these variables predicted the outcome of BMI at each age. We examined the impact of race and socioeconomic status (SES), both associated

with child adversity, on the effect of maternal depressive symptoms on daughter's BMI. In this way, we were able to test for potential effect modification and arrive at three base models reflecting the interaction between maternal depressive symptoms with child self worth, child TV viewing, and SES, with daughter's BMI. Additive interaction was modeled using dummy variables based on median cutoff values for each of the three effect modifiers: 4.1 hours of TV/video viewing; child's self worth score of 3.1, and SES (low or moderate versus higher SES). Adjusting for race strengthened the model and was included in final models.

Maternal Factors: Deciding to Include/Exclude in Models

Mother's BMI appeared to be a very strong predictor of child's BMI in later adolescence. We explored effect modification by this variable by creating, modeling, and comparing the association between the following categories and late adolescent BMI: (a) low depression, low BMI; (b) low depression, high BMI; (c) high depression, low BMI; and (d) high depression, high BMI. The effect of maternal BMI was on late adolescent BMI and did not differ according to the presence of maternal depressive symptoms, so we concluded that there was not

effect modification by maternal BMI. We later tested it as a potential causal intermediate in our final models but did not retain it in the final models.

Maternal smoking status at the time of the exposure was also examined. Mother's smoking was strongly correlated with many other variables such as socioeconomic status, race, and TV watching. Since it was not a confounder and did not improve model fit, we did not retain it in the final models.

Final Mixed Linear Models

In the first set of analyses, we used mixed linear models to look at change in BMI over time throughout the 10 years of the study period during adolescence, based on the levels of maternal depressive symptom score. We tested different covariance matrix assumptions in the mixed models, including unstructured (UN, used in the SES and self worth models below), and compound symmetric (CS) for the model, and auto regressive (or AR-1, used for the TV model below) and selected the parameter that best fit each model. To see if these differences were significant, we compared the difference in overall p-values of girls in low to moderate, moderate to high, low to high maternal depressive symptom groups.

We retained the following variables in our final mixed linear models of the outcome of daughter's BMI:

(1) race + maternal depressive symptom category x socioeconomic status

(2) race + maternal depressive symptom category x television/video hours/day

(3) race + maternal depressive symptom category x child self worth

Final General Linear Models

Using the information from the mixed linear models, we selected the strongest model to proceed with (the TV model #2 from the Final Mixed Linear Models) and tested SES and child self worth as potential causal intermediates. We then tested child depression, maternal BMI, and child's BMI at baseline as potential causal intermediates on separate mechanistic pathways as well. We note that maternal BMI was considered as a potential causal intermediate here because it could be argued that the maternal depressive symptom exposure was already present before the actual measurement of the symptoms, and could be conceived as preceding maternal BMI.

4.3 Results

To determine the extent of the relationship between exposure to maternal depressive symptoms and later adolescent BMI of their daughters, we used multivariable models to explore maternal depressive symptoms and different variables which could modify or mediate the effect of maternal depressive symptoms on daughter's BMI. These models include a range of variables that reflect constructs from Figure 4.1, such as child diet and activity, demographic factors, family mealtime behaviors, mother's health, and the child's psychosocial state.

Baseline Characteristics

Table 4.1 shows that child depression tends to increase along with mother's depression. There was a tendency for having less family meals together and a shorter duration of family meals amongst daughters of mothers who were more depressed. Averaged physical activity of the girls from ages 9-17 decreased linearly for girls whose mothers were more depressed. Child's depression score was also directly linearly associated with mother's depression score and self-worth decreased linearly with increases in mother's depression score. Girls of moms with higher depressive symptom scores were less likely to dine together

and had shorter family meals. Child's BMI at ages 18-20 exceeds 24 kg/m^2 at the 85th percentile of the CDC's growth curves for overweight BMI: 24.5 ± 5.8 kg/m^2 in daughters of mothers with low depression, 25.7 ± 6.9 kg/m^2 for the category of moderate depressed moms, and 25.8 ± 7.2 kg/m^2 for daughters of highly depressed mothers. Mother's BMI was also linearly associated and increased alongside increased depression score.

Table 4.1 – Descriptive Characteristics of Subjects by Mother's Depression Symptom Score

Subject Characteristics	Maternal Depressive Symptoms		
	Low [8] (n=634)	Moderate [8] (n=458)	High [8] (n=165)
	column % *or* mean ± s.d.		
SES [1,2]			
Low	**15.3%**	**20.3%**	**22.4%**
High	**41.0%**	**40.2%**	**26.1%**
Age at Exam 1 (yrs)	**10.0 ± 0.6**	**10.1 ± 0.6**	**10.0 ± 0.6**
Child Physical Activity Score (METS) [3]	**20.5 ± 9.9**	**20.0 ± 10.1**	**19.1 ± 10.5**
Child TV/Video (hrs/day) [3]	**4.39 ± 2.2**	**4.4 ± 2.1**	**4.6 ± 1.9**
Child % Energy from Discretionary Fats, added sugar [3]	**41.0 ± 5.2**	**41.5 ± 5.3**	**41.3 ± 5.5**
Child % Energy from Saturated Fat [3]	**12.7 ± 1.7**	**12.9 ± 1.7**	**13.2 ± 1.6**
Healthy Eating Index 2015 Score [3]	**44.8 ± 7.2**	**44.2 ± 7.6**	**43.9 ± 7.0**
DASH Dietary Pattern Score [3]	**3.8 ± 0.6**	**3.8 ± 0.6**	**3.8 ± 0.6**

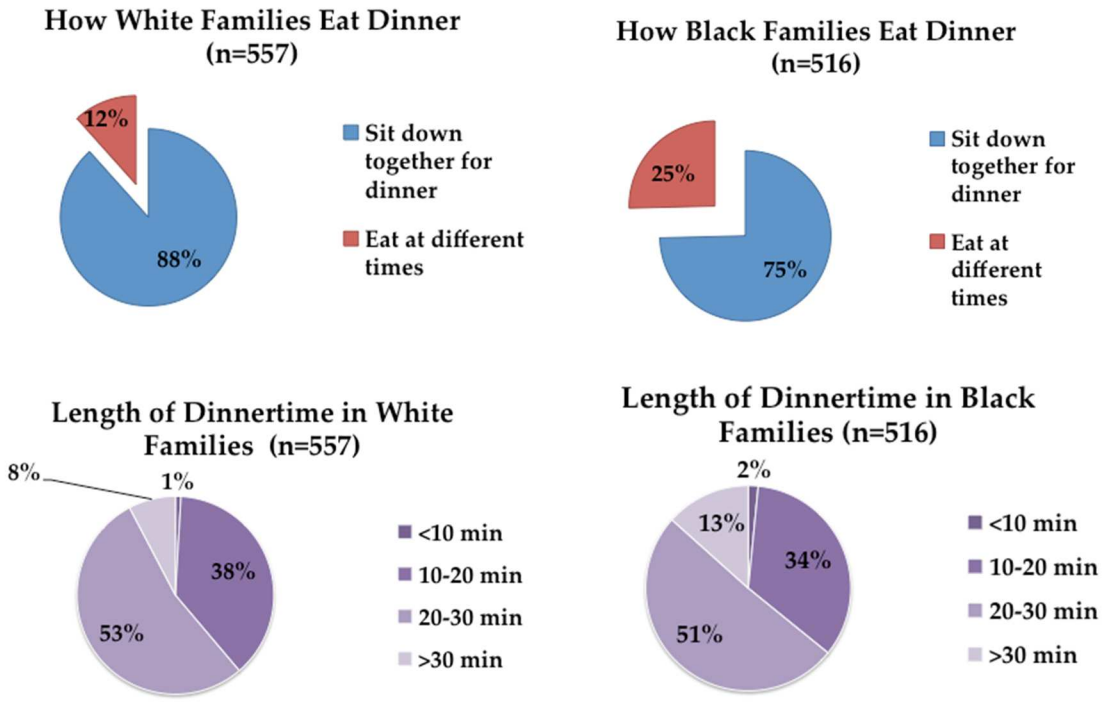
Child BMI (kg/m^2) at Baseline [4]	**18.4 ± 3.6**	**18.8 ± 4.1**	**18.9 ± 3.7**
Child BMI (kg/m^2), ages 18-20 yrs	**24.8 ± 6.1**	**25.7 ± 6.9**	**26.1 ± 7.2**
Mother's Depressive Symptom Score [5,8]	**18.7 ± 2.1**	**23.2 ± 1.1**	**28.3 ± 2.7**
Mother's BMI (kg/m^2) [5]	**26.7 ± 6.8**	**27.3 ± 6.7**	**27.9 ± 7.3**
CESD Depression Score (Child) [6]	**12.3 ± 8.9**	**13.5 ± 8.9**	**16.5 ± 10.5**
Self Worth Score (Child) at Exam 1 [7]	**3.2 ± 0.6**	**3.2 ± 0.6**	**3.2 ± 0.6**
Self Worth Score (Child) at Exam 9	**3.3 ± 0.6**	**3.2 ± 0.7**	**3.1 ± 0.7**

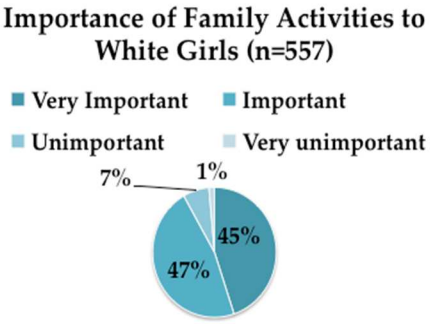
[1] Low=income <$20,000 and ≤high school or income <$10,000; high=income ≥$40,000 and >high school; moderate=those not qualifying as low or high [2] Socioeconomic status [3] Average from ages 9-17 [4] Baseline, first available: from exam 1 or 2 [5] Maternal variables from the only available single baseline measure [6]CESD Depression Score (Child) Ranges from 0 to 53, low to high (study exam 10). [7] Self Worth (Based on Harter Scale) ranges from 1 to 4, low to high self worth. [8] Range of Mother's depressive symptom scores: [Low: 9-21][Moderate: 22-25][High: 26-39].

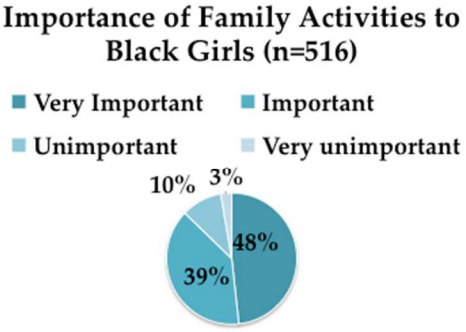
There were both similarities and differences across races with respect to family mealtime practices. Most families of the girls ate dinner together with the family (88% of white girls; 75% of black girls) and the Mantel-Haenszel chi square test showed that the difference between those who ate together in contrast to those who ate at different times for both races was significant ($p<0.0001$). The duration of dinner for most families, regardless of race, lasted from 20-30 minutes, followed by 10-20 minutes with significant differences

between categories of responses (p=0.05). Most white and black girls rated family activities as very important or important. There were a higher percentage (10% vs. 7%) of black girls who rated family activities to be unimportant compared to white girls respectively, however the difference was not statistically significant (p=0.5787). Of these family mealtime characteristics, only the way families ate dinner was associated with maternal depressive symptoms (Spearman Correlation Coefficient = 0.12).

Figure 4.4 – Descriptive Family Mealtime Characteristics



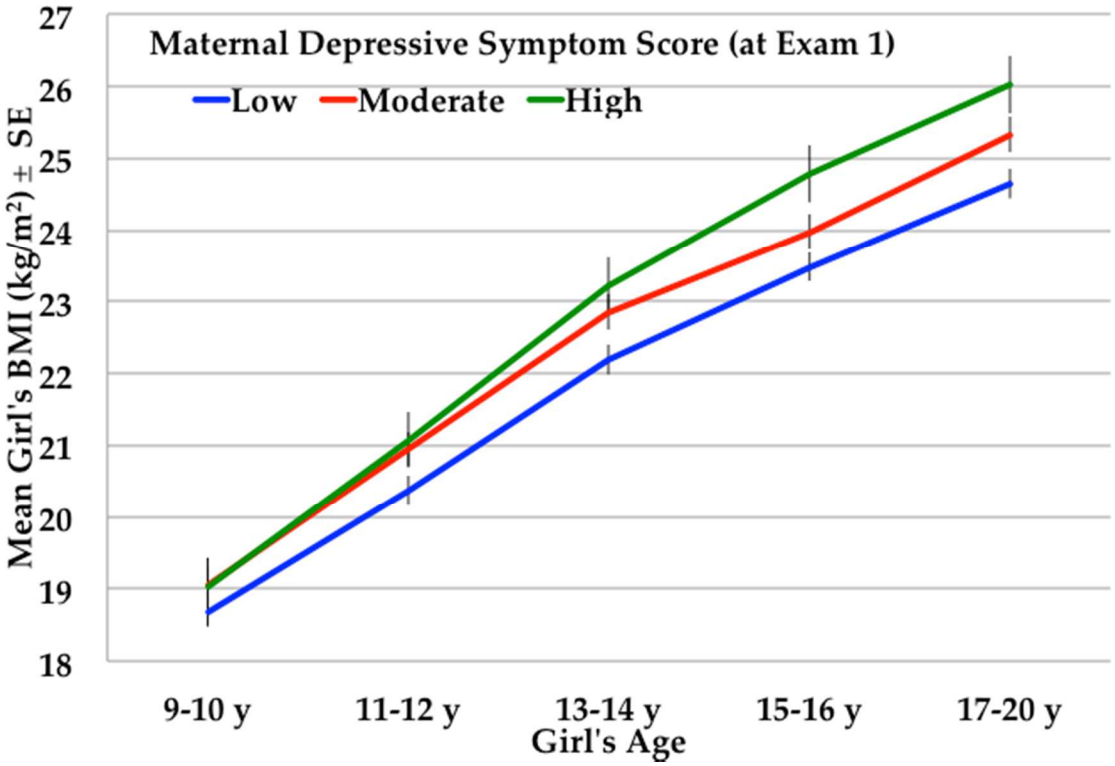




To describe the basic relationship between maternal depressive symptoms and daughter's BMI, we first looked at how BMI changed over time according to level of maternal depressive symptoms (Figure 4.5). BMI in the moderate and high depressive symptom groups diverged gradually throughout adolescence. The 9-10 year-old daughters of mothers with the lowest depression scores maintained the lowest BMI levels throughout adolescence and those whose mothers had the highest depression scores had the greatest increases in BMI ($p=0.0238$, Figure 4.5). It appears that the differences in BMI accumulated throughout adolescence such that daughters of mothers with higher depressive symptoms experienced greater increases in BMI overall compared to those with lesser depressive symptoms over 10 years. At the end of follow-up, 17-20 year-old girls whose mothers had higher depression scores had a BMI that was 1.37 kg/m^2 higher than girls whose mothers had low scores ($p=0.03$). This difference is

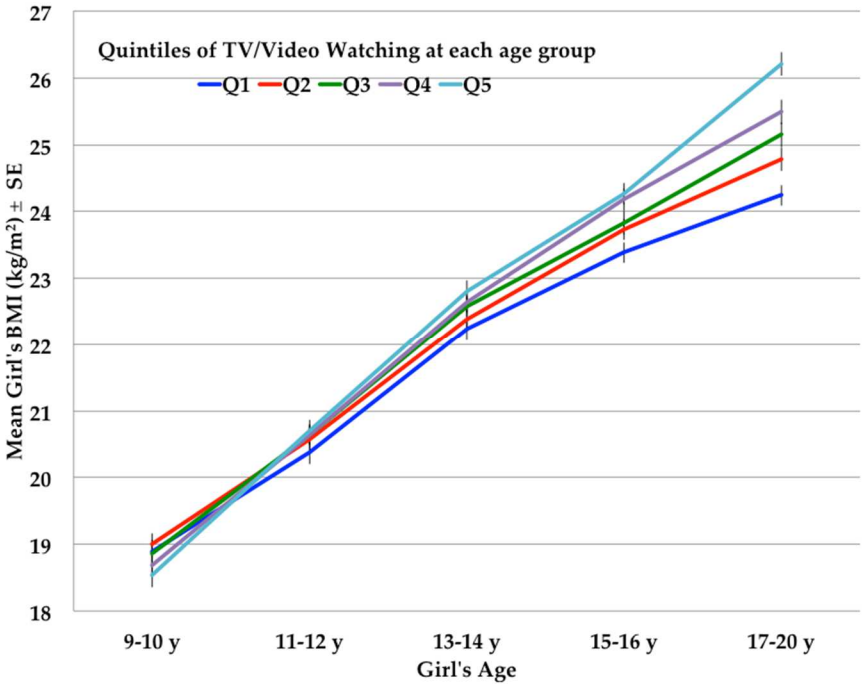
particularly evident in the 17-20-age range, with significant differences between low-to-moderate (p=0.03) and low-to-high (p=0.002) maternal depressive symptom groups.

Figure 4.5 – Daughters of mothers with higher depressive symptoms have greater BMI compared to those with lower depressive symptoms by late adolescence *Adjusted for race

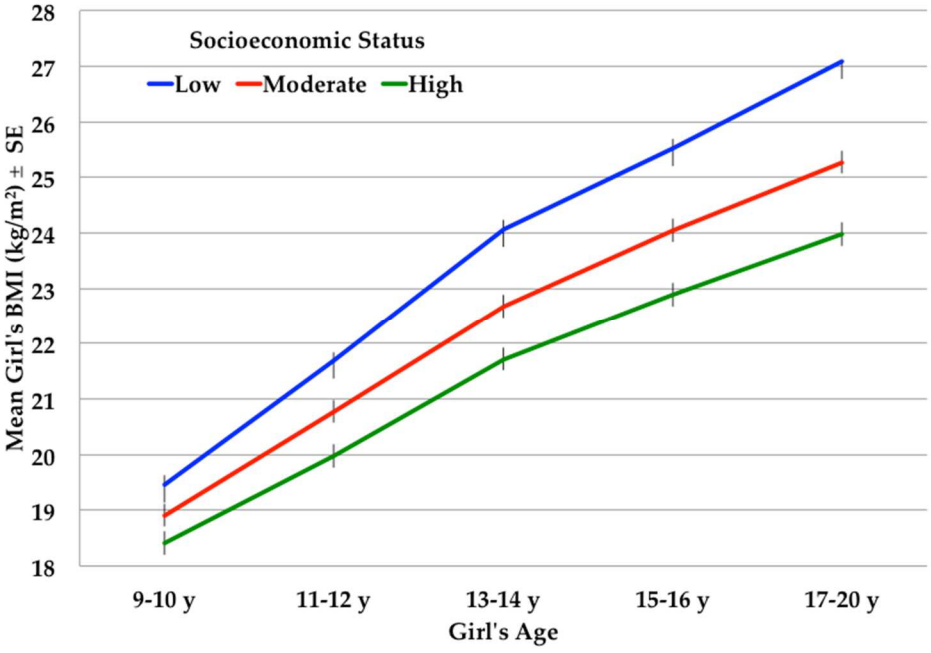


Next, we explored the relationship between various risk factors for obesity and continuous BMI since these factors were considered as potential confounders in the analyses. BMI increased across adolescence and when compared across quintiles of TV-watching categories, we saw the greatest increases in BMI in later adolescence, especially among heavy TV watchers (Figure 4.6A). The effect of SES on BMI similarly widened in later years, with girls from lower SES families maintaining a higher BMI than those who have higher levels of SES throughout adolescence (Figure 4.6B). Girls who have higher self worth (in Q4 and Q5 quintiles) tended to maintain lower BMI throughout adolescence (Figure 4.6C). Unlike with SES and TV, with the effect of level of child self worth status on BMI is maintained across ages without major change in particular years.

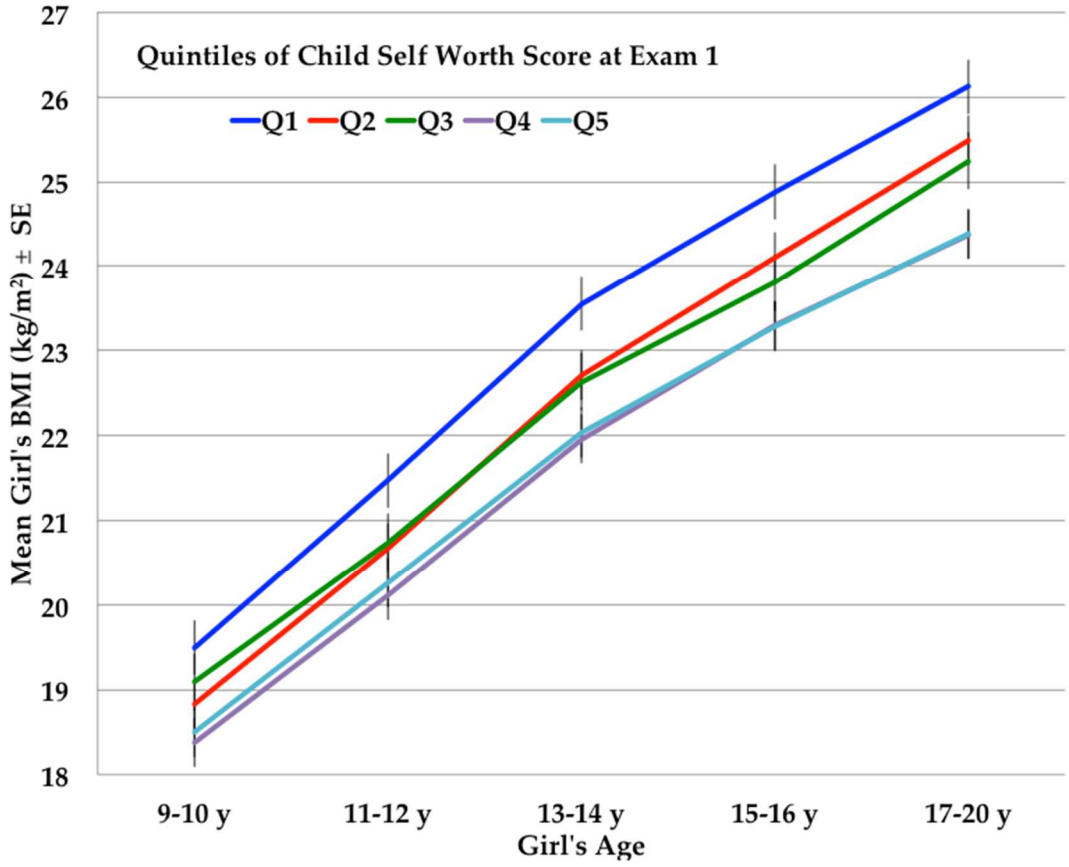
Figure 4.6. Mixed Linear Models of TV, SES, Child Self Worth with BMI from 9-21 years **All panels adjusted for race. n=1487*



A.



B.



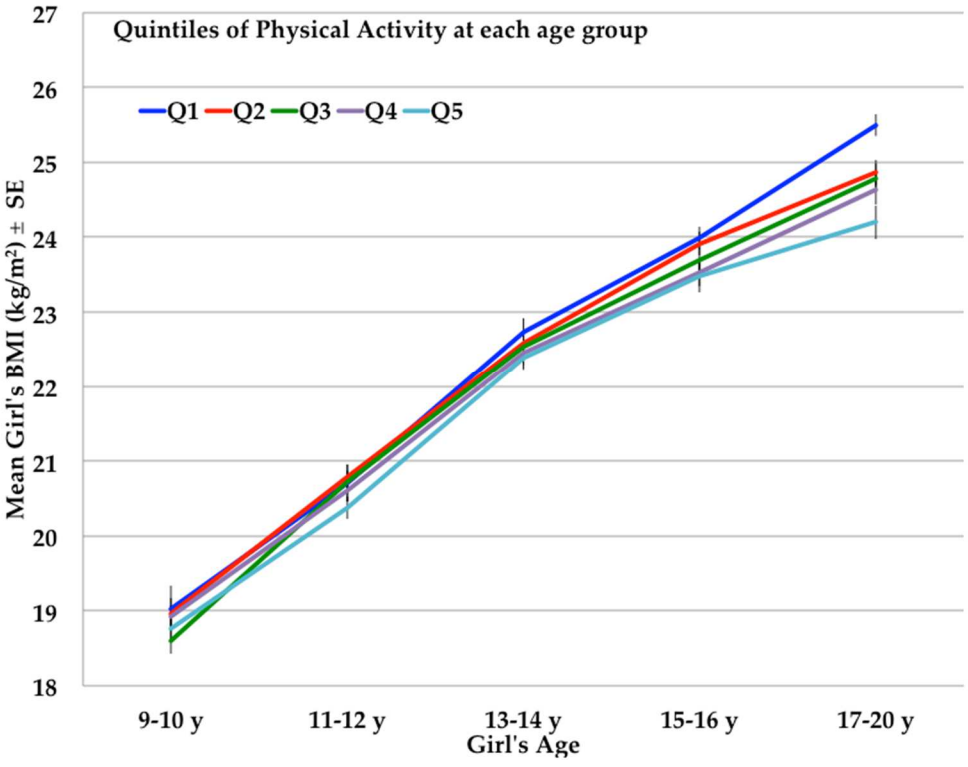
C.

There were other factors, physical activity and estimates of diet quality and of a healthier diet pattern, which were of interest as possible mechanisms by which maternal depressive symptoms could modify daughter's BMI. Physical activity's association with BMI did not differ significantly across quintiles \until girls reached 17-20 years, when those who were in Q1 with the lowest levels of activity were shown to have higher BMIs compared with those in higher quintiles of activity (Figure 4.7A). For future models, we did include activity as a potential confounder and instead explored the potential modification of maternal

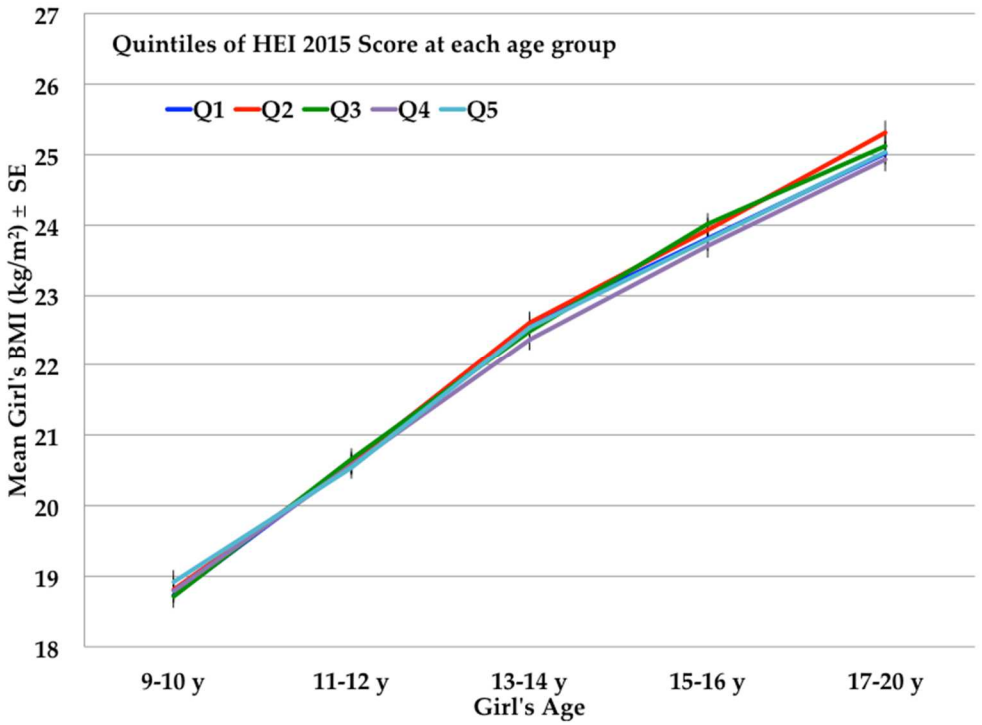
depressive symptoms by the hours TV/video watched per day as an estimate of sedentary behavior. There was also no relationship between HEI-2015 and a slight relationship with the DASH eating pattern and daughter's BMI over time (Figure 4.7B,C).

Figure 4.7. Mixed Linear Models of Physical Activity, HEI-2015, DASH Diet with BMI from 9-20 years **All panels adjusted for race. n=1487*

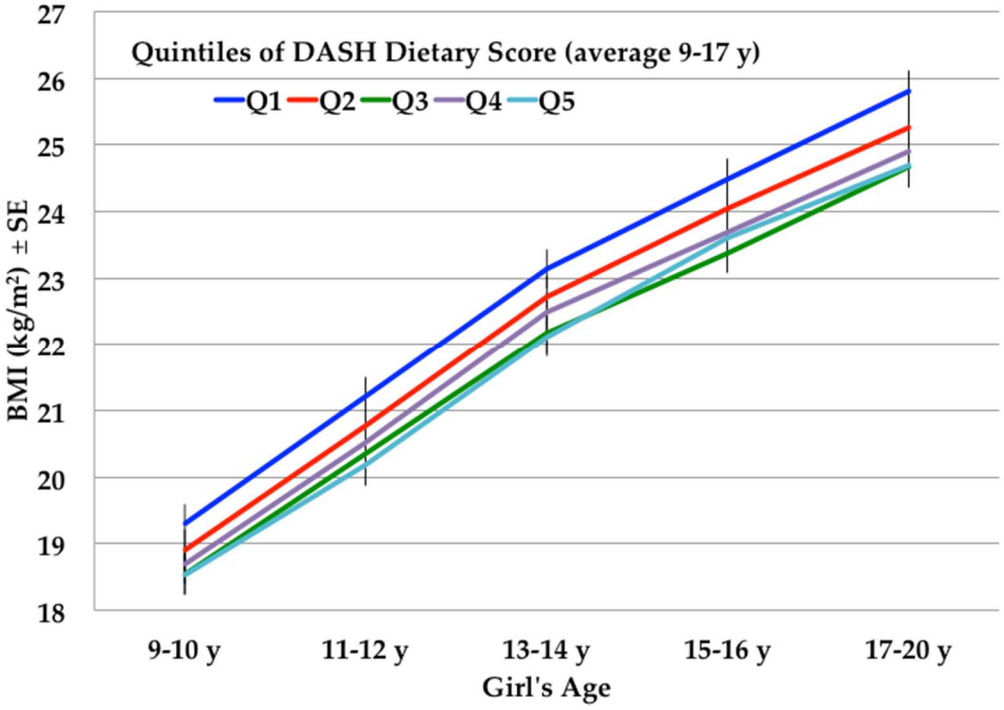
A.



B.


Quintiles of HEI 2015 Score at each age group
Q1 Q2 Q3 Q4 Q5
Mean Girl's BMI (kg/m²) ± SE
27
26
25
24
23
22
21
20
19
18
9-10 y
11-12 y
13-14 y
15-16 y
17-20 y
Girl's Age

C.

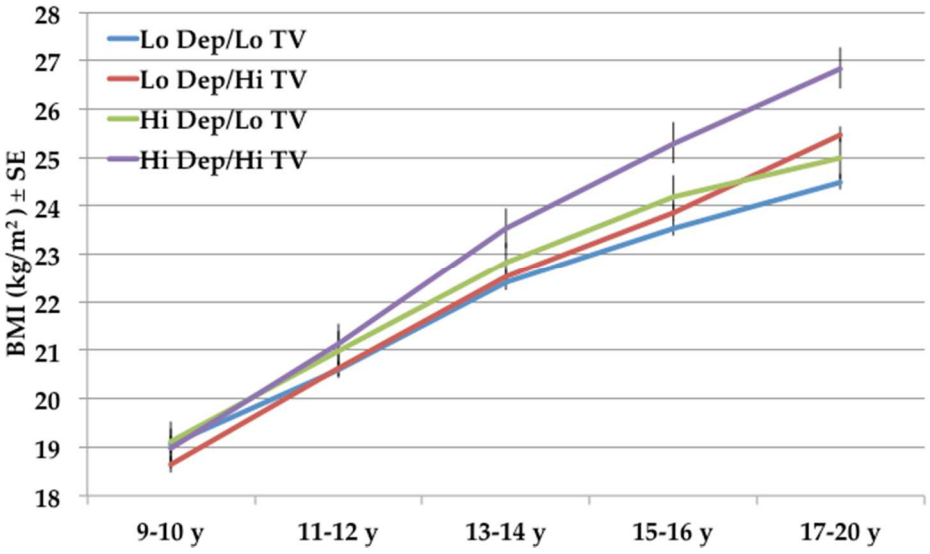

Quintiles of DASH Dietary Score (average 9-17 y)
Q1 Q2 Q3 Q4 Q5
BMI (kg/m²) ± SE
27
26
25
24
23
22
21
20
19
18
9-10 y
11-12 y
13-14 y
15-16 y
17-20 y
Girl's Age

Our final mixed linear models included interaction terms reflecting modification of the effect of mother's depressive symptoms on daughter's BMI by TV, SES, and child's self-worth, respectively (Figure 4.8); these were selected based on an exploration of potential effect modification by a larger number of variables that were explored in Figures 4.6 and 4.7. There appeared to be a greater cumulative effect of either TV and SES in combination with mother's depressive symptoms on daughter's BMI over time, an effect which was less apparent with the combination of maternal depressive symptoms and self worth: this trend is similar to what was observed with these factors alone in Figure 4.6. The combined effects of higher TV watching, lower self worth, or lower SES on daughter's BMI among those with mothers with higher depressive symptoms were all statistically significant ($p<0.0001$). The BMI level among girls with higher TV watching and whose mothers had more depressive symptoms was statistically significantly higher ($p=0.0053$) than the BMI seen among those with lesser depressive symptoms ($p=0.0026$) (Figure 4.8A). Having a mother with higher levels of depressive symptoms among those with lower SES was statistically significant to a lesser degree ($p=0.0397$) (Figure 4.8B). Among those

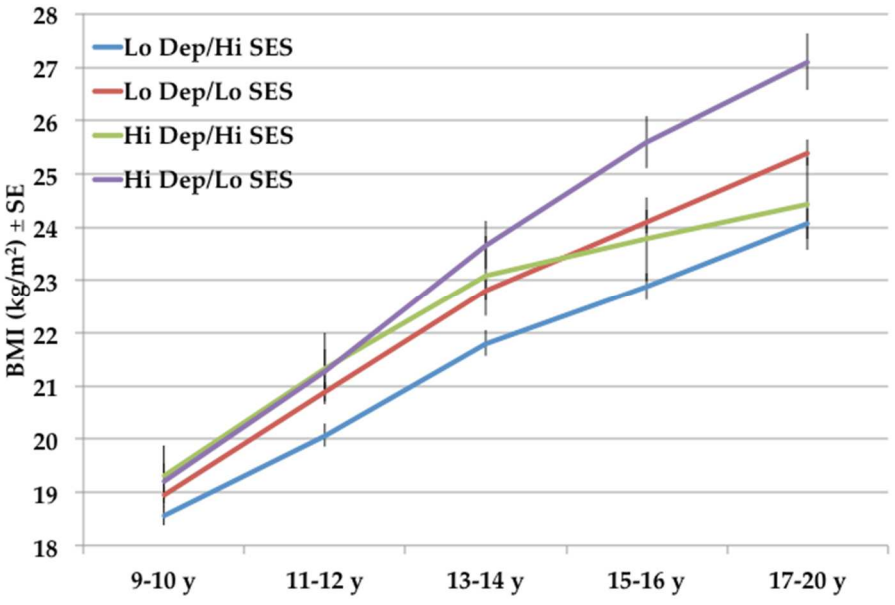
girls with mothers who had lower levels of depressive symptoms, having lower SES also had a statistically significant effect on their BMI ($p=0.0014$) (Figure 4.8B). Figure 4.8C shows that both maternal depressive symptoms alone and low levels of self-worth (in the daughters) were associated with a higher BMI throughout adolescence; however, those girls with low levels of self-worth who also had mothers with more depressive symptoms had even greater increases in BMI over time than those with either risk factor alone. Girls who remained the leanest throughout adolescence were those with higher levels of self-esteem whose mothers had few depressive symptoms.

Figure 4.8. The effects of mother's depressive symptoms on child BMI throughout adolescence is modified by daughter's TV viewing, self worth, and SES. **All panels adjusted for race, n=1252.*

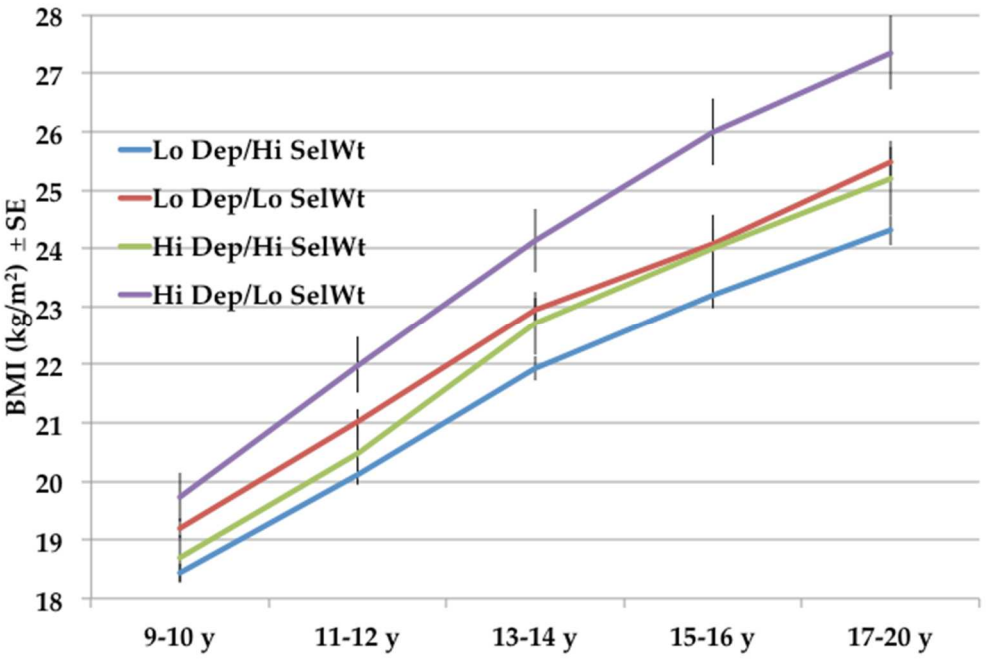
A.



B.



C.



We explored the outcome of child's BMI at age 18 in multiple linear regression models (Table 4.2) to confirm that there was no confounding due to diet or family meal factors we examined earlier in Figure 4.7. In Table 4.2, we demonstrate that the addition of race to the model improves the R^2 and model fit, which we included in all of our models. To build our final multiple linear models, we referred to our insights from mixed linear modeling in Figure 4.6A and 4.8A where TV viewing modified the effect of maternal depressive symptoms on daughter's BMI throughout adolescence.

Table 4.2. Daughter's BMI at ages 18-20 adjusting for Diet (HEI-2015 or DASH) or family dinner together factors

n=1257	Child BMI at 18 y ± SE				
Maternal Depressive Symptoms	Unadjusted	Race-Adjusted	Model 1A	Model 1B	Model 2
Low [n= 634]	24.8 ± 0.3	24.8 ± 0.3	24.8 ± 0.3	24.8 ± 0.3	24.8 ± 0.3
Moderate [n=458]	25.7 ± 0.3	25.7 ± 0.3	25.7 ± 0.3	25.7 ± 0.3	25.7 ± 0.3
High [n=165]	26.1 ± 0.5	26.2 ± 0.5	26.2 ± 0.5	26.2 ± 0.5	26.2 ± 0.5
R^2	0.006	0.06	0.07	0.07	0.07
p-trend	0.0057	0.0027	0.0033	0.0031	0.0026

Model 1A: Adjusted for race, physical activity (average from 9-17y), Healthy Eating Index Score (average from 9-17y)

Model 1B: Adjusted for race, physical activity (average from 9-17y), DASH dietary pattern score (average from 9-17y)

Model 2: Adjusted for race, family dinner together/apart at exam 1

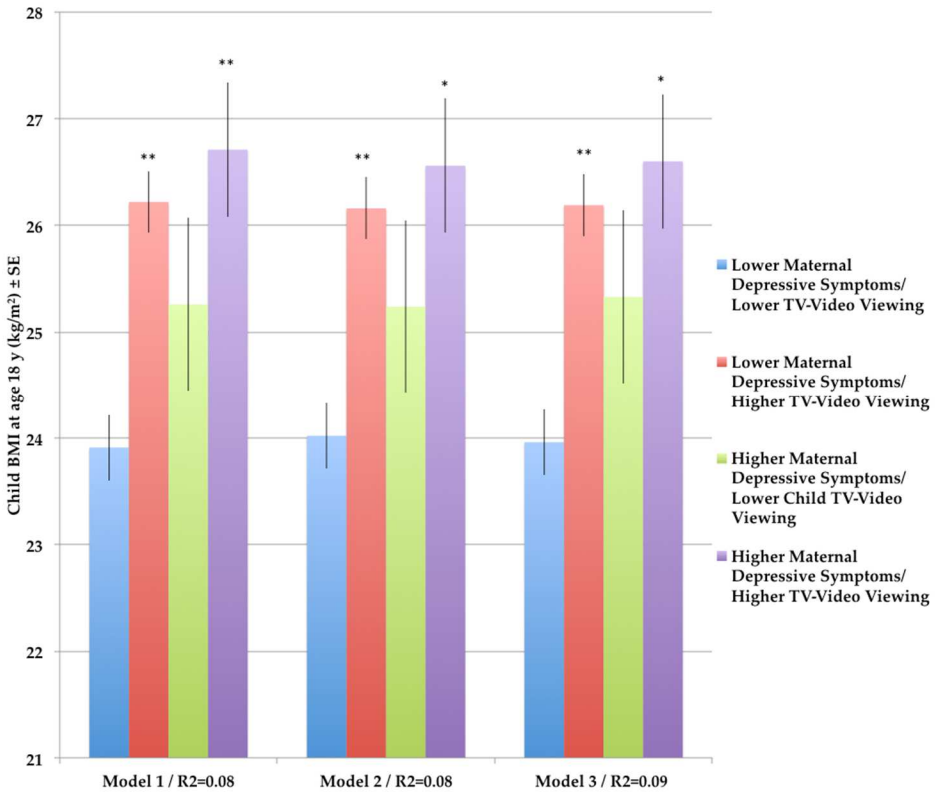
Modeling maternal depressive symptoms x TV-viewing demonstrated the strongest effect on daughter's BMI at age 18 (R^2=0.08) when compared with that a

model of maternal depressive symptoms x child self worth (R^2=0.07), or maternal depressive symptoms and SES (R^2=0.06). We proceeded with the model of maternal depressive symptoms x TV viewing in following model-building steps considering the roles of potential causal intermediates. In Figure 4.9, we evaluated SES and child self worth separately as potential causal intermediates of the relationship between average child TV viewing (ages 9-17) x exposure to maternal depressive symptoms (at baseline, exam 1). Comparing Model 1 (base model) to Model 2 (adjusting for SES) and Model 3 (adjusting for child self worth) showed that the effect did not change significantly between models with the addition of SES of child self worth. Consistent significant differences were shown between girls who watched more TV-Video and the referent groups within each model, regardless of their mother's level of depressive symptoms ($p<0.0001$ for Lower Maternal Depressive Symptoms). Model 3 is a slightly better predictive model, with an R^2=0.9 compared to R^2=0.8 of Models 1 and 2, although the change in effect was similar between models.

In a separate subset analysis in Figure 4.10, the effect of maternal depressive symptoms with effect modification by TV on daughter's BMI at ages 18-20 is attenuated with the additions of maternal BMI, child depression, or child

baseline BMI, but these factors do not completely explain the effect. For example, the combined effect of maternal depression and higher TV watching on child BMI at ages 18-20 is attenuated with the addition of maternal BMI (Δ=2.83 to 2.51kg/m^2), child depression (Δ=2.81 to 1.6 kg/m^2), or child baseline BMI (Δ=2.45 to 1.81 kg/m^2) to the models. Figures 4.11 and 4.12 are separate subset analyses restricted to show if maternal BMI, child depression, or child baseline BMI affect the relationship between maternal depressive symptoms with SES or child self worth respectively, on daughter's BMI at ages 18-20. We see that adding maternal BMI, child depression, or child baseline BMI attenuate the effect slightly, but any one of these factors do not completely explain the effect. Individually, child baseline BMI and maternal BMI appear to be strongly predictive of daughter's later BMI and could also be causal intermediates, strengthening the strength of association between the exposures and outcome of daughter's BMI at age 18 (for example, Figure 4.11: Model 5A, without baseline child BMI: R^2=0.06; Model 5B, with baseline child BMI: R^2=0.63; Figure 4.12: Model 6A, without maternal BMI: R^2=0.06; Model 5B, with maternal BMI: R^2=0.14).

Figure 4.9. Evaluation of SES and Child Self Worth (at exam 1) as potential causal intermediates of the combined effects of maternal depressive symptoms and TV-video viewing on child BMI at ages 18-20 y *



Model 1: Adjusted for race.

Model 2: Adjusted for race + SES.

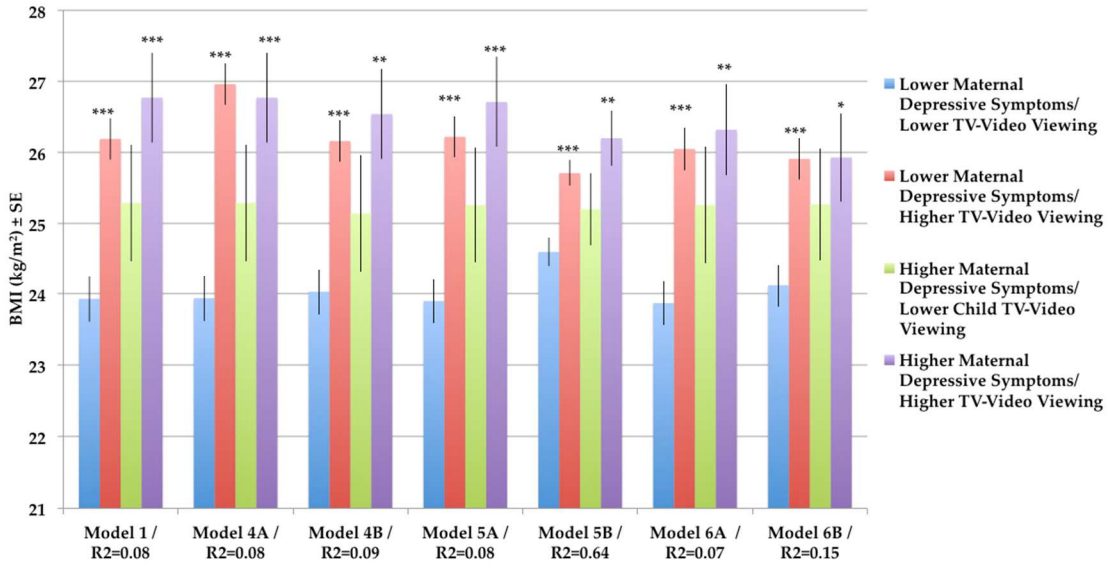
Model 3: Adjusted for race + child self worth exams 1.

p values compare categories within each model to the corresponding referent group (Lower Maternal Depressive Symptoms/Lower TV-Video Viewing)

* $p<0.001$;

** p<0.0001

Figure 4.10. Evaluation of Child Depression (exam 10), Child BMI (baseline), and Maternal BMI as potential causal intermediates of the combined effects of maternal depressive symptoms and TV-video viewing on Child BMI at 18-20 y



Model 1: Adjusted for race.

Model 4A (without child depression) **& 4B**: Adjusted for race + child depression at exam 10.

Model 5A (without child BMI) **& 5B**: Adjusted for race + child BMI at baseline earliest of exams 1 or 2/10.

Model 6A (without maternal BMI) **& 6B**: Adjusted for race + maternal BMI at baseline.

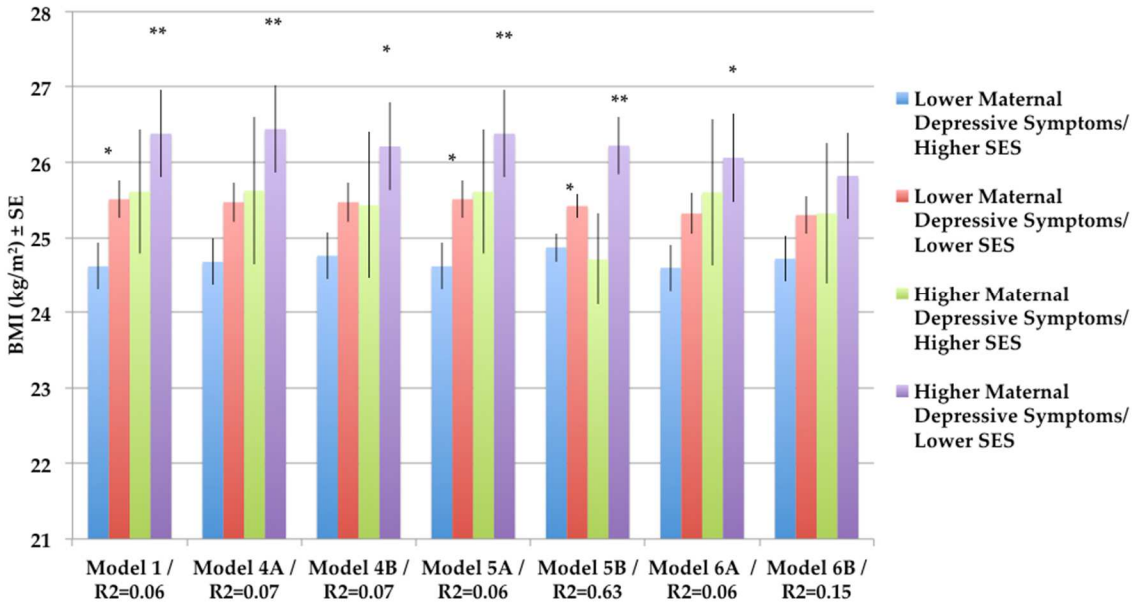
p values compare categories within each model to the referent group (Lower Maternal Depressive Symptoms/Lower TV-Video Viewing)

* p<0.01;

** p<0.001;

** p<0.0001

Figure 4.11. Evaluation of Child Depression (exam 10), Child BMI (baseline), and Maternal BMI as potential causal intermediates of the combined effects of maternal depressive symptoms and SES on Child BMI at 18-20 y *



Model 1: Adjusted for race.

Model 4A (without child depression) & **4B**: Adjusted for race + child depression at exam 10/10.

Model 5A (without child BMI) & 5B**:** Adjusted for race + child BMI at baseline earliest of exams 1 or 2/10.

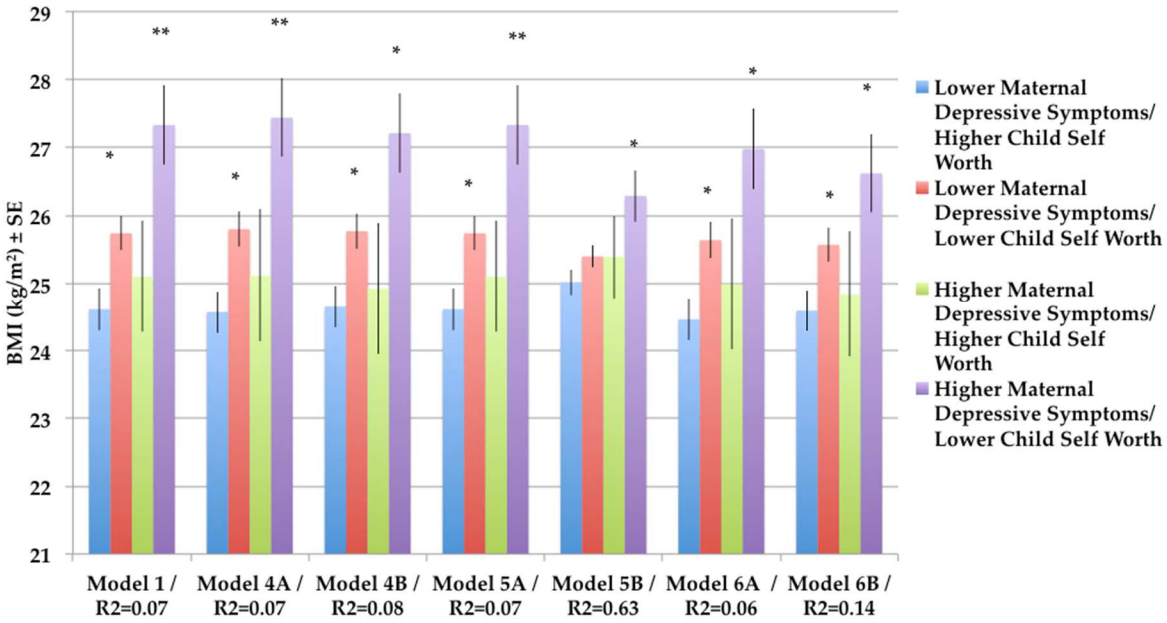
Model 6A (without maternal BMI) & **6B**: Adjusted for race + maternal BMI at baseline.

p values compare categories within each model to the referent group (Lower Maternal Depressive Symptoms/Higher SES)

* $p<0.05$;

** $p<0.01$

Figure 4.12. Evaluation of Child Depression (exam 10), Child BMI (baseline), and Maternal BMI as potential causal intermediates of the combined effects of maternal depressive symptoms and Child Self Worth on Child BMI at 18-20 y *



Model 1: Adjusted for race.

Model 4A (without child depression) & **4B**: Adjusted for race + child depression at exam 10.

Model 5A (without child BMI) & **5B**: Adjusted for race + child BMI at baseline earliest of exams 1 or 2.

Model 6A (without maternal BMI) & **6B**: Adjusted for race + maternal BMI at baseline.

p values compare categories within each model to the referent group (Lower Maternal Depressive Symptoms/Higher Self Worth Viewing)

* $p<0.01$;

** $p<0.001$

Maternal Depression Symptoms, Child Depression, and Child Obesity

Mother's BMI was correlated with child BMI and overweight at both baseline (0.30) and at the end of follow up (0.33), but was not correlated with mom's depression symptom score (0.05). Child's depression score and mother's depressive symptom score were only weakly correlated (0.13). Since mother's BMI is not highly correlated with mother's depressive symptoms, but is correlated with child BMI or overweight in early and in later adolescence, it is likely that mom's BMI may affect child overweight by having the same diet, same obesogenic environmental exposures, and genetics.

Mother's depression when the child is young affects child's depression, and later child obesity, and may do so conceivably through family mealtimes and diet quality, although further study is needed. Mothers are the first influence in deciding on meals (66%) of the time (children, 22%), and in

preparing them 71% of the time (children, 16%). Grandparents, sisters, brothers, and fathers were all significantly less involved in these mealtime decisions. These models suggest socio-ecological "phenotypes" for the kinds of social and environmental factors within the family that could be useful targets for obesity prevention interventions in children.

4.4. Discussion

Our major findings in this study are that *1)* early adolescent exposure to high levels of maternal depressive symptoms is a risk factor for the greatest increases in adolescent BMI compared to exposure to low levels of maternal depressive symptoms, throughout and in late adolescence *2)* among those individuals exposed to high levels of maternal depressive symptoms, higher self-worth and lower depression among girls may interrupt the progression of weight gain resulting in increases in late adolescent BMI, *3)* TV-viewing is one important modifiable lifestyle behavior which compounds the effect of exposure to high levels of maternal depressive symptoms on late adolescent BMI. Diet and dining together as a family did not confound these observations. Adjusting for potential causal intermediates, such as child's depression, child self worth, maternal BMI, or child's baseline BMI attenuated the effect of maternal

depression, but did not fully explain the way that maternal depressive symptoms affect daughter's BMI. This study importantly draws attention to the importance of the psychosocial environment within families and to maternal depressive symptoms as a source of toxic stress to adolescent girls with physiological and health consequences.

Other predictors of the relationship between maternal depressive symptoms and child obesity risk included unhealthy foods with saturated fat or discretionary calories, family mealtime practices, sedentary behavior. We identified factors that appear to be a combination of useful, modifiable predictors - perhaps even more relevant today with the rise of a culture tied to devices, quick and on-the-go meals, and busy schedules for children and families. Screen time is an increasingly relevant concern today for its possibility to reduce physical activity and increase sedentary behavior among youth today with the widespread availability of portable mobile devices, enabling TV to accompany virtually any activity. Early overweight in childhood is a very strong predictor of later obesity, but it is not the only predictor and may be particularly important in the context of other psychosocial or dietary risk factors. Mother's BMI, more so than mother's depression alone, is a predominant predictor of daughter's BMI

and could be explored in future studies in conjunction with child's diet and psychosocial factors. The role of maternal BMI is complicated, however, and will be discussed further as a limitation below.

Considering environmental and demographic factors like race, SES, and sedentary behavior in our models in part explained some of child overweight. If our goal were to build a predictive model if toxic stress from psychosocial and socio-environmental sources, we might consider SES as a separate source of toxic stress. SES may be a contributor to maternal depression, so we look at it separately as an effect modifier and not in conjunction with maternal BMI. Adjusting for SES may in that instance artificially diminish any true effect of exposure to maternal depression on child BMI. Additionally, our study sample offers a single record of SES for the family. This is a limitation, as it does not account for changes in SES that could occur over the 10 years of follow-up. The possible interaction between SES and depression is notable: for instance, depression could lower the overall ability of a family to support themselves and improve their SES, but low SES and challenging circumstances, potentially from other sources of toxic stress could also independently contribute to depressive symptoms. Or, both could occur at different times. Future studies should

consider accounting for changes in SES and depression status in designs of their assessments.

Low self worth is a modifiable risk factor that incidentally plays a significant role in modulating the effect of exposure to maternal depression on daughter's BMI. By contrast, controlling for child's depression did not much explain the differences in BMI across maternal depressive symptom exposure groups. One explanation for this may be that a child's higher sense of self-worth may operate as a buffer to stressful exposures on the pathway between exposure to maternal depressive symptoms in early adolescence and later adolescent obesity. The role of self-worth may be a marker for internal resilience that could buffer the stressful effects of maternal depression and protect from the child from experiencing depression herself. Child self-worth and child depression are negatively correlated (-0.43), such that having higher self-worth is associated with lower child CESD depression score. These may be potential mechanistic actors on pathways mediating the relationship between maternal depressive symptoms and child's obesity (Figure 4.1).

Race and SES are risk factors that are not modifiable. Combined with disparities associated with race or socioeconomic status, inherently challenging environments characterized by complex demands on a mother's time and health could have far-reaching intergenerational health effects. The most important issues for mothers could certainly have far-reaching effects on the physical and mental health and wellbeing of their children in more difficult environments. Here, we draw attention to existing challenges for mothers related to depression and overall maternal health, and propose that others who seek to address child health outcomes be cognizant of and address environmental challenges, and consider ways to offer resources to combat the challenges related to SES that interfere with a mother's capacity to care for their children.

Mother's health – gaps in care

While assessing a child's health and well-being, pediatric clinicians may also wish to pay attention to maternal depression. Symptoms of depression, including feeling depressed or anxious, trouble getting up, frequent crying, irritation, tiredness or anger, or sleeplessness are all behaviors that may arise around young children, beginning as early as during the prenatal period. While post-partum care for mothers is a priority in countries in Asia or Europe, in the

United States, there are significant limitations in awareness and coverage of this care for mothers(223); addressing post-partum care could be an important policy step to make maternal depression a modifiable risk factor for child health, of course, improving the mental and physical health outcomes of new mothers as well.

The causes for depression can be sourced in the environment, but also may have genetic origins; animal(224) and clinical(225) studies have identified methylation patterns in genes, such as Bdnf (brain-derived neurotrophic factor), related to brain plasticity and endocrine regulation, which can distinguish between depressed or non-depressed individuals in a population. More questions remain: if there is a strong relationship between maternal health disparities and child health outcomes, how does it operate? Whether child obesity risk is primarily due to shared genetics with a depressed or overweight mother, or challenging child-rearing conditions in the case of a stressful psychosocial environment, requires further investigation. New research models should consider contextual factors that may differentially affect maternal depression in particular racial, ethnic, and economic groups.

Possible Biological Basis for Stress Exposure Related Child Obesity

Animal studies of neuronal morphology suggest that even with short-term exposure to stress, sexually dimorphic effects (226) in areas relevant to stress response regulation and cognitive performance are observable (227). It is unknown if these effects might explain a part of a child's diet choices and decision-making capacity upon exposure to stress. When the child's physical stress response is no longer tolerable, it becomes toxic (69) and physiological changes may occur to the neuroendocrine system with potential metabolic consequences. Cumulative stress from exposure to chronic adversity elevates CRH (corticotropin releasing hormone) and elevates inflammatory cytokines, activates the parasympathetic system, and is also involved in regulating food intake. Stress activation of cortisol release disrupts food intake regulation by stimulating neuropeptide Y and blunting the effect of leptin that could in turn result in long-term increases in energy intake and body fat accumulation. Chronic stress interacts with mechanisms of energy intake and expenditure and may contribute to overweight and obesity(70).

The adverse effects of earlier pubertal timing associated with characteristics of the family psychosocial environment have not gone unnoticed:

Boyce et al. describe the consequences of such trends with evidence of how psychopathology and life experiences may underpin physiological changes in pubertal timing. A number of studies in that review pointed to family cohesion, for instance, as a factor which is associated with later pubertal timing in girls, whereas instability prompted earlier puberty(179). The relationship between family environmental stress and child health risks manifests in disparities in physiological factors, like age at menarche, which consequently have been shown in prior chapters to predict metabolic outcomes. The roles of additional forms of family stress on intermediates that affect metabolism are an additional direction for further mechanistic query.

A Possible Pathway - maternal limitations and creation of an obesogenic environment

Our study points to a significant contribution of maternal depressive symptoms in creating an obesogenic environment where elevated BMI and any associated obesity risk accumulate over adolescence. We sought to carefully examine psychosocial factors that may affect interactions between mothers and their daughters. Our findings may help others to posit possible frameworks in which these factors might challenge healthy eating occasions and result in adverse health risks for these girls. Women with depression are not as likely to

engage in enriching activities with their children(228). Family meals have been shown in a longitudinal study(229), Project EAT(74), to protect against the development of child obesity, although mechanisms are uncertain(25,230–232) - some studies suggest it is primarily diet quality(233,234) and not frequency of family meals that predicts obesity risk. The implications of this are great; toxic stress may potentiate childhood adversity and be manifested in pathogenesis of health disparities in growing children.

Context for intergenerational health disparities

Garcia et al.(235) describe a need for research pertaining to the context of child development that articulates how variables such as racism, prejudice, discrimination, and other sources of environmental difficulties impact developmental outcomes. Other disparities are worthy of note, such as racial differences in child obesity risk, in obesity-related health outcomes, and in both maternal and child perinatal outcomes. Black women are twice as likely to experience maternal health problems compared to white women(236). Births in black women have greater preterm birth rates, infant mortality, and birth weight. The causes for this disparity are not well understood and are likely complex;

accounting for income, chronic health conditions or risky behaviors did not eliminate this disparity(237).

Strengths and limitations of our analysis

One limitation of our analysis is that it is difficult to tease apart the contribution of genetics versus nurture that may mediate mother's maternal health impact in their daughters due to limited data in NGHS pertaining to the mothers' health. Mother's BMI could relate to child BMI through shared genetics, as well as shared environment. Additional attention to changes and causes for change in maternal BMI in future studies could add valuable insights to parse out the contributions of genetics or environment to child BMI. We also do not know how long mothers were depressed, and cannot definitively determine the sources of depression. It is difficult to separate out the role of maternal BMI in how maternal depressive symptoms might contribute to her daughter's BMI, overweight, or obesity risk. We are unable to ascertain if mothers exhibit depressive symptoms because of her own overweight due to poor diet or exercise, or if she is depressed because she is overweight from genetics, or a combination of behavior and genetics. A mother-child data-driven approach would be useful to deeply understand the causal motivating factors behind

cardiometabolic risk in children exposed to maternal depression. Brain imaging of depressed mothers, in combination with data on bonding and depressed responsiveness of mothers to their children shows that there remains a lot to learn about root causes for maternal depression, and whether or how these might be passed down.

One interesting basic science study describes a potential biological target for resilience – Bdnf – that when blocked, appears to buffer the effects of chronic stress(238). A recent study of second-trimester women who underwent amniocentesis identified Bdnf, cortisol, and cortisone stress hormones in amniotic fluid(239). Bdnf was unrelated to glucocorticoid concentrations however glucocorticoid concentrations were associated with low socioeconomic status. Whether this ability to buffer stress and exhibit resilience is an attribute that can be passed down inter-generationally remains to be defined. More neuroscience-based evidence may bring about new targets to consider for both maternal and child health interventions.

A second limitation in this cohort is that by lacking repeated measures of maternal depressive symptoms after the initial survey when girls were 9-10 years

old, we are unable to distinguish between the prolonged effect of exposure to depression, and potential importance of chronicity and early exposure to maternal depressive symptoms as we suggest here. Today, more comprehensive methods for evaluating maternal depression exist that may still be comparably simple to the one used here. We also did not have information about any concurrent psychiatric conditions. Using improved assessment tools along with repeated measures, future investigators – even perhaps clinicians collecting family history – could identify vulnerable populations and screen for and monitor maternal depression. More longitudinal evidence – in both boys and girls - with rigorous measures of depression, anxiety, and the context of mental health symptomology is needed to best show the degree to which maternal depression and its potential influence on family meals may elevate child obesity risk, and determine if risk is sex-specific.

Our study supports the notion that maternal depressive symptoms have more widespread and long-term effects on child health and nutrition and may even set a trajectory for unhealthy behaviors of children growing into young adulthood. While we do not yet understand all the root causes of maternal depression, or the constructs within which they may affect a mother's own health

or that of her child, we are able to say that early exposure to maternal depressive symptoms is associated with the child's sense of self-worth and depression, and predicts increased risk of obesity as a young adult. Future work may test the roles of poor family mealtime practices and poor diet patterns in children as potential modifiable nutrition and lifestyle behavior intermediary constructs that may be on the pathway to increased risk.

To better understand the mechanisms for the impact of Adverse Child Experiences on health outcomes, future studies should consider incorporating measures of social and environmental sources of toxic stress as well as collecting biomarkers associated with stress and chronic inflammation. Cortisol and C-reactive protein, or metabolic hormone levels of ghrelin or leptin are examples of hormones that reflect stress-induced physiological and behavioral changes and could provide important insights to support psychosocial ratings in both mothers and daughters, such as those collected from depression scales. Studies in a diverse cohort of mother-child dyads as units could strengthen qualitative evidence of how maternal depression operates. Further, following them over time for later cardiometabolic health outcomes would add a supportive dimension of a biological, measureable outcome to current knowledge.

Identifying the pressure points on mothers to alleviate risk in their children

Interventions geared towards supporting child health, which takes maternal depression and maternal health into account may actually provide the foundation for long-term health of the child. Children develop within a socio-environmental framework, a unique context. Research which leads to the development and building of the capacities of both mothers and daughters in their shared and respective environments to achieve optimal health would be invaluable. This work identifying the role of maternal depressive symptoms in daughter's health is important for pediatric clinicians to be aware of, because a pediatrician may be the first point of contact for mothers who experience depression – perhaps due to socio-environmental limitations - and who may not have the resources to visit their own practitioner first. While clinicians assess for signs of abuse and neglect of their young patients, we suggest that clinicians also be on alert for maternal depression. The resulting interventions will need to take into account maternal risk factors, the impact of these on childhood obesity, and fundamentally address the mother-daughter dyad as a unit of practice. This will require cooperation and collaboration across multiple sectors, including many stakeholders in the healthcare industry.

Further study is required to tease apart the effects of un-modifiable factors in the family environment such as race or SES, and modifiable ones, such as dietary or family mealtime behaviors. One might argue that the psychosocial factors, including exposure of maternal depression, or child's depression or self worth, could be modifiable with the right systemic support for families who have greater challenges. NGHS has a wealth of behavioral data around family life and mealtime behaviors that others may wish to explore to identify additional family environmental factors that may impact child obesity risk, and potential pathways by which they might operate.

CHAPTER FIVE: Discussion, Implications, and Future Directions

5.0 Discussion

Overall Summary of Results

This dissertation provides new insights into the identification of early, modifiable predictors of cardiometabolic risk and impacts of family-based stress on child obesity. The work in Chapters 2 and 3 present that early body composition measures are useful predictors of later lipid levels, as does a later adolescent cardiovascular risk outcome associated with chronic disease comorbidities. In Chapter 3, we explore the unique, sensitive period of development in adolescence: pubertal maturation is involved in many hormonal and physiological changes to a young girl's body that may mediate health status or the manifestation of risk factors.

It is imperative that disease prevention researchers continue to find new, effective ways to address gaps in the current knowledge by looking for specific, modifiable links between physically measureable risk factors and a holistic measurement of the health of a child's environment in which she grows up in. To understand the health of a young girl is to also be fully cognizant that each one is in a unique context that interacts with her genetics during normal physical and

biological development. If this interaction occurs in sensitive periods, of which adolescence is one, and which is also more difficult to study, it stands to make girls more vulnerable to accumulation of risk during adolescence.

In Chapter 3, post-menarche BMI measures were better predictors of later LDL, HDL, TG, and TG/HDL than pre-menarche body fat measures in both white and black girls, but body fat measures as early as pre-menarche are predictive in black girls. After menarche, when girls of both races are mature, pubertal maturation can no longer account for racial differences in obesity or other related risk factors of interest. Clinicians could take early measures of simple anthropometric measures of body fat, such as BMI and WC, to screen pediatric patients and monitor ones who have other lifestyle or dietary characteristics consistent with a dyslipidemic or atherosclerotic risk profile. This result is consistent with prior work and knowledge of the effects of pubertal maturation on body composition, but also adds the additional insight of racial differences in efficacy of early adolescent body fat measures at predicting later adolescent lipid levels.

By leveraging a nationally representative data set alongside rigorous methods and knowledge of some of these environmental effects, our objective is to identify better targets for comprehensive preventative interventions for cardiometabolic conditions. In Chapters 2 and 3, we examined patterns in physical, clinically measureable body fat predictors of later cardiometabolic risk and then in Chapter 4, we broadened our scope and explored the association of body fat with factors in the socio-environmental context of these girls that could be associated with young adult obesity at age 18.

Several investigators have drawn attention to the need for more research tying maternal mental health, studied in the complex context of the family home environment, to health outcomes in children(58,64,240,241). Whether during the first 1,000 days of an infant's life, or later on in adolescence, a mother's influence is one of the prime influential factors that cultivate healthy behaviors in children during many critical developmental periods. To our knowledge, a paucity of studies have touched upon maternal mental health and correlated it with only a limited selection of child health outcomes; these studies were mostly done in pre-school age children, and were cross-sectional. Not enough studies have been

done to demonstrate a consensus in adolescents. Thus, the availability of this large data sample including data for both mothers and their children, followed prospectively, with a wealth of socio-environmental, nutrition, and physiological measures, makes completing this project valuable. It offers the possibility of constructing a more complete story to help explain racial differences in the development of obesity-related dyslipidemia and other associated cardiometabolic risks.

Indeed, Chapter 4 revealed that high levels of maternal depressive symptoms are associated with late adolescent obesity in their daughters. Among those individuals exposed to high levels of maternal depressive symptoms, a plausible intermediate that may modulate the effect of childhood exposure to maternal depression involves the child's own psychosocial status. Higher self-worth and lower depression among girls may attenuate the sustained progression of weight gain associated with exposure to maternal depressive symptoms. In turn, these relationships may also reflect modifiable eating behaviors and the social context of healthy or disordered eating. Unhealthy diet patterns and consumption of calorie-dense foods and sedentary behavior are modifiable variables that are involved in the context of girls exposed to their

mother's depression. Maternal depression in itself is a modifiable exposure today. At the time of data collection in this NGHS cohort, however, it is not unreasonable to think that stigma around mental health and depression may have made it difficult for a mother to self-identify as depressed and to seek assistance.

Many more studies are needed to delve into the mechanisms by which maternal depression may affect child overweight, some of which may follow routes described in Figure 4.1. Future work should also establish standards for measurement and identification of exposure to risk from Adverse Child Experiences, which include maternal mental health. Predictors of maternal mental health, through its influence on family meals and lifestyle factors including child diet quality, may give rise to the development of cardiometabolic disease and obesity.

While studies of individual predictors of cardiometabolic risk provide a useful means to inform a clinician's advice, there is also merit to looking at longitudinal models of cardiometabolic risk to inform prevention and identify those at high risk early enough to intervene. Although such models exist but are

limited in quantity in adults, there is a need for a model that begins to look at risk factors earlier in the lifespan, specifically in children and adolescents. It is often a composite of factors that elevates an individual's risk of disease. Thus, we contribute these findings in an adolescent population of black and white girls that could also be tested in other populations and possibly lead to the systematic development of a cardiometabolic risk model. General limitations of this work are that NGHS is not representative of a specific population, and does not necessarily represent a national or contemporary American population. Our findings only apply to girls, and cannot be generalized to adolescents in general. However, prevalence of overweight and obesity in NGHS match those of NHANES for a number of years(114), so any of our findings may also be able to be replicated in other cohorts of adolescent females.

In summary, this dissertation addresses a critical gap in knowledge about predictors of racial disparities in adolescent risk of obesity and cardiometabolic diseases; it does so by utilizing extensive information from multiple constructs that are important to child health, including measures of maternal mental health, and physical body fat measures that we found to predict biological risk factors typically serving as markers for poor cardiometabolic outcomes. This

dissertation work is positioned to encourage other investigators to consider a life-course approach for primary prevention of racial disparities in adverse child health outcomes (195). As we suggest in Chapter 4, starting early to strengthen caregiver capacities to promote knowledge, attitudes, and behaviors associated with optimal health of their child may ameliorate the transmission of intergenerational disease risks.

Currently, child obesity disparities research largely lacks the evidence required to advise the update of adolescent risk factor guidelines. However, the story built here, with interconnected links of specific dietary, socio-environmental, and biological predictors in a large biracial cohort, affords an opportunity to impact this scarcity of evidence. Consideration of early body composition, menarche age, and exposure to Adverse Childhood Experiences, along with racial differences in risk would be valuable additions to screening for obesity-related risk outcomes in adolescents.

Moreover, there are complicating factors, not the least of which is maternal depression, which has detrimental effects on a child, and contributes to health disparities for women. This in turn adversely affects the communities in

which they live and work. We focus on only one Adverse Child Experience (maternal depression), however other sources of toxic stress that could expose a child to risk include exposure to violence, maltreatment, parental substance use, negative life events, parental incarceration, discrimination, bullying, economic hardship, and community violence. Some of these are modifiable, like BMI and weight status (through lifestyle diet or physical activity modifications), or exposures to toxic stress (by buffering effects of a supportive adult caregiver and resources to strengthen a child's sense of self-worth and self-esteem) and some are dictated by constraints related to socioeconomic status, for example. In any case, it is necessary to understand how ACEs operate and if resiliency measures are effective (and by how much) at buffering exposure to toxic stress in the family and home environments.

Implications for future interdisciplinary work

A complex set of risks such as those described through this research requires a sophisticated response. There is a need for cities and workplaces to support caregivers by offering services, for laws that protect their healthcare needs, for clinicians who are trained to screen for depression and monitor the perinatal and postnatal needs of the mothers. This is especially important in

populations with increased risk of health disparities, such as low-income families or those who are racial or ethnic minorities or have other risks such as living in areas with hazards like crime or violence. In these environments, risk of maternal depression and stresses are greater, and the consequences of intergenerational risk passed down are also expansive.

The question remains: while there is a need for resources that focus on the mother, who can or should provide them? If a child experiences her mother's depression, what can a school or clinic or after-school program offer to cultivate resilience and support a lifetime of healthy behaviors and choices? Our hope is that this paper draws attention to an important aspect of child health that pertains to a key person – the mother - that is understudied and overlooked as it pertains to child health. While this leads to more questions, the potential is great to engage stakeholders in economics, medicine, public health, and government to learn from the past and support child health in the future.

We expect this work will help to bring to light critical targets for primary prevention of future racial, ethnic, or socioeconomic disparities in obesity and chronic metabolic diseases. The move for personalized medicine for treatment

extends to personalized prevention. Improving our understanding of resilience and modifiable risk factors that act in the immediate environment of the child will contribute in powerful ways in tailoring interventions to leverage and complement broader, less specific one-size-fits-all policies

APPENDIX

A.2.3. Ranges of BMI, WC, %BF and WHR for each quintile according to race

	W	B		W	B
BMI (kg/m²)			**WC (cm)**		
Q1 [n=145W 118B]	[11.2 < 15.7]	[12.9 < 15.7]	Q1 [n=155W 109B]	[49.0 < 57.7]	[50.0 < 57.6]
Q2 [n= 139W 124B]	[15.7 < 17.1]	[15.7 < 17.1]	Q2 [n=131W 131B]	[57.7 < 61.0]	[57.8 < 61.0]
0Q3 [n=132W 132B]	[17.2 < 18.8]	[17.2 < 18.8]	Q3 [n=131W 133B]	[61.1 < 65.1]	[61.1 < 65.1]
Q4 [n=118 145B]	[18.8 < 21.6]	[18.8 < 21.6]	Q4 [n=121W 143B]	[65.2 < 72.5]	[65.2 < 72.5]
Q5 [n=81W 182 B]	[21.7 < 35.0]	[21.7 < 35.2]	Q5 [n=77W 185B]	[72.7 < 99.3]	[72.7 < 115]
%BF (%)			**WHR**		
Q1 [n=44W 219B]	[15.4 < 18.7]	[5.1 < 18.7]	Q1 [n=114W 149B]	[0.66 < 0.77]	[0.66 < 0.77]
Q2 [n=128W 135B]	[18.7 < 22.3]	[18.7 < 22.3]	Q2 [n=128W 135B]	[0.77 < 0.79]	[0.77 < 0.79]
Q3 [n=169W 95B]	[22.4 < 25.8]	[22.4 < 25.7]	Q3 [n=130W 134B]	[0.79 < 0.81]	[0.79 < 0.81]
Q4 [n= 156W 107B]	[25.8 < 30.6]	[25.8 < 30.5]	Q4 [n=127W 136B]	[0.81 < 0.83]	[0.81 < 0.84]
Q5 [n=118W 145B]	[30.6 < 43.6]	[30.6 < 47.0]	Q5 [n=116W 147B]	[0.84 < 0.97]	[0.84 < 0.97]

Table A.4.1. Correlations between Exposure, Outcome, and Co-Variables

Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Mother's Depression Score																
2. Child's Depression Score[1]	0.20															
3. Child's Self Worth[1]	-0.09	-0.46														
4. Race	0.01	0.05	0.18													
5. SES[2,3]	-0.08	-0.10	-0.03	-0.31												
6. Average (ages 9-17) TV Watching (hrs)[4]	0.05	0.11	0.03	0.63	-0.36											
7. Height at First Exam (cm)	0.00	0.05	-0.04	0.24	0.02	0.12										
8. Mother's BMI (kg/m²)	0.09	0.11	-0.05	0.27	-0.09	0.25	0.15									
9. Child's BMI (kg/m²) (9-10 yrs)	0.06	0.11	-0.10	0.17	-0.06	0.25	0.35	0.28								
10. Child's BMI (kg/m²) (at 18 yrs)	0.07	0.10	-0.12	0.19	-0.11	0.30	0.26	0.33	0.80							
11. Length of Evening Meal[5,6]	-0.05	-0.01	0.02	0.05	-0.01	0.01	-0.02	-0.01	0.01	0.03						
12. Family Eats Together (Y/N)[6]	0.19	0.07	0.04	0.19	-0.08	0.14	0.10	0.10	0.07	0.06	-0.16					
13. Importance of family to child[7]	-0.03	-0.01	-0.04	0.02	0.04	-0.01	0.04	-0.05	0.03	-0.01	0.02	-0.005				
14. Child % energy from discretionary fats, alcoholic	0.03	-0.01	0.05	0.20	-0.16	0.25	0.05	0.13	-0.03	-0.02	-0.06	0.10	0.007			

beverages, added sugar[4]																
15. Child Whole Grain servings[4]	0.01	-0.08	0.04	-0.07	0.05	-0.08	0.02	-0.06	-0.05	-0.07	-0.01	0.03	0.021	-0.16		
16. Child % Energy from Saturated Fat[4]	0.08	0.04	0.01	0.09	-0.19	0.19	0.04	0.07	0.04	0.05	-0.02	0.04	0.01	-0.13	0.35	

Pearson Correlation Coefficient

Spearman Correlation Coefficient

[1]CESD Depression Score (Child) Ranges from 0 to 53, low to high (study exam 10). Self Worth (Based on Harter Scale) ranges from 1 to 4, low to high self worth (study exam 9).

[2] Low=income <$20,000 and ≤high school or income <$10,000; high=income ≥$40,000 and >high school; moderate=those not qualifying as low or high [3] Socioeconomic status [4] Average from ages 9-17

[5] Score: Length of evening meal low scores=1 (from <10 min) to higher scores=4 (>30 min) [6]earliest measure, at study exam 1 [7]earliest measure, at study exam 2

Journal Abbreviations

Acad Nutr Diet	Academy of Nutrition and Dietetics
Acta Paediatr	Acta Paediatrica
Adolesc Pediatr Gynecol	Adolescent and Pediatric Gynecology
Adv Child Dev Behav	Advances in Child Development and Behavior
Am Heart J	American Heart Journal
Am J Cardiol	American Journal of Cardiology
Am J Clin Nutr	American Journal of Clinical Nutrition
Am J Epidemiol.	American Journal of Epidemiology
Am J Hum Biol	American Journal of Human Biology
Am J Obstet Gynecol	American Journal of Obstetrics and Gynecology
Am J Prev Med	American Journal of Preventive Medicine
Am J Public Health	American Journal of Public Health
Ann Clin Psychiatry	Annals of Clinical Psychiatry
Ann Epidemiol	Annals of Epidemiology
Ann Hum Biol	Annals of Human Biology
Annu Rev Nutr	Annual Review of Nutrition
Anthropol Anz	Anthropologischer Anzeiger – Journal of Biological and Clinical Anthropology

Arch Gen Psychiatry	Archives of General Psychiatry
Arch Pediatr Adolesc Med	Archives of Pediatric and Adolescent Medicine
Biol Psychiatry	Biological Psychiatry
Biomed Res Int	BioMed Research International
BJOG	British Journal of Obstetrics and Gynaecology
BMC Pediatrics	BMC Pediatrics
BMC Public Health	BMC Public Health
BMJ	BMJ: British Medical Journal
Br J Health Psychol	British Journal of Health Psychology
Br J Nutr	British Journal of Nutrition
Can J Diet Pract Res	Canadian Journal of Diabetic Practice and Research
Child Dev	Child Development
Child Obes	Childhood Obesity
Clin Psychol Sci Pract	Clinical Psychology and Science Practice Journal
Curr Diab Rep	Current Diabetes Reports
Dev Psychol	Developmental Psychology
Dev Psychopathol	Developmental Psychopathology
Diabetes Vasc Dis Res	Diabetes and Vascular Disease Research

Diabetol Metab Syndr	Diabetology and Metabolic Syndrome Journal
DMS Journal	Diabetes and Metabolic Syndrome Journal
Econ Hum Biol	Economics and Human Biology Journal
Endocr Pr.	Endocrine Practice
Epidemiol Rev.	Epidemiologic Reviews
Ethn Dis	Ethnicity and Disease
Eur J Clin Nutr	European Journal of Clinical Nutrition
Eur J Nutr	European Journal of Nutrition
Health Place	Health and Place
Health Psychol.	Healthy Psychology
Horm Behav	Hormones and Behavior
Hypertens	Hypertension
Int J Cardiol	International Journal of Cardiology
Int J Environ Res Public Health	International Journal of Environmental Research and Public Health
Int J Epidemio	International Journal of Epidemiology
Int J Obes	International Journal of Obesity
Int J Obes Relat Metab Disord	International Journal of Obesity Related Metabolic Disorders
Int J Pediatr Obes	International Journal of Pediatric Obesity

J Acad Nutr Diet	Journal of the Academy of Nutrition and Dietetics
J Adolesc Heal	Journal of Adolescent Health
J Affect Disord	Journal of Affective Disorders
J Aging Health	Journal of Aging and Health
J Am Acad Child Adolesc Psychiatry	Journal of the American Academy of Child and Adolescent Psychiatry
J Am Coll Cardiol.	Journal of the American College of Cardiology
J Am Coll Nutr	Journal of the American College of Nutrition
J Am Diet Assoc	Journal of the American Dietetic Association
J Clin Endocrinol Metab	Journal of the Clinical Endocrinology and Metabolism
J Clin Epidemiol	Journal of Clinical Epidemiology
J Diabetes Res	Journal of Diabetes Research
J Health Soc Behav	Journal of Health and Social Behavior
J Hum Nutr Diet	Journal of Human Nutrition and Diet
J Lipid Res	Journal of Lipid Research
J Natl Med Assoc	Journal of the National Medical Association
J Neurosci	Journal of Neuroscience
J Nutr Educ Behav	Journal of Nutrition Education, and Behavior

J Pediatr	Journal of Pediatrics
J Perinat Educ	Journal of Perinatal Education
J Reprod Med	Journal of Reproductive Medicine
JAMA	Journal of the American Medical Association
Matern Child Health J	Maternal and Child Health Journal
Med Sci Sports Exerc	Medicine and Science in Sports and Exercise
Mol Psychiatry	Molecular Psychiatry
N Engl J Med	New England Journal of Medicine
Nat Rev Neurosci	Nature Reviews. Neuroscience
Neuroimage	NeuroImage
Neurology	Journal of American Academy of Neurology
Nutr Hosp	Nutricion Hospitaliaria
Nutr Metab Cardiovasc Dis	Nutrition, Metabolism and Cardiovascular Diseases
Obes Rev	Obesity Reviews
P R Health Sci J	Puerto Rican Health Science Journal
Pediatr Clin North Am	Pediatric Clinics of North America
Pediatr Diabetes	Pediatric Diabetes
Pediatrics	Pediatrics

Physiol Behav	Physiology and Behavior
PLoS One	PLoS One
Prev Med	Preventive Medicine
Proc Natl Acad Sci U S A	Proceedings of the National Academy of Sciences of the United States of America
Psychol Bull	Psychological Bulletin
Psychol Med	Psychological Medicine
Psychoneuroendocrinology	Psychoneuroendocrinology
Soc Neurosci	Society for Neuroscience
Soc Res Child Dev	Society for Research in Child Development
Soc Sci Med	Social Science and Medicine
Stat Med	Statistics in Medicine
Trends Cogn Sci	Trends in Cognitive Science
Trends Neurosci	Trends in Neuroscience
Women Health	Women's Health

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